

# **EXHIBIT 255**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use BOOSTRIX safely and effectively. See full prescribing information for BOOSTRIX.

**BOOSTRIX (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed)**  
**Suspension for Intramuscular Injection**  
**Initial U.S. Approval: 2005**

**INDICATIONS AND USAGE**

BOOSTRIX is a vaccine indicated for active booster immunization against tetanus, diphtheria, and pertussis. BOOSTRIX is approved for use as a single dose in individuals 10 years of age and older. (1)

**DOSAGE AND ADMINISTRATION**

A single intramuscular injection (0.5 mL). (2.2)

**DOSAGE FORMS AND STRENGTHS**

Single-dose vials and prefilled syringes containing a 0.5-mL suspension for injection. (3)

**CONTRAINDICATIONS**

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any tetanus toxoid-, diphtheria toxoid-, or pertussis antigen-containing vaccine or to any component of BOOSTRIX. (4.1)
- Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous pertussis antigen-containing vaccine. (4.2)

**WARNINGS AND PRECAUTIONS**

- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.1)
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk of Guillain-Barré syndrome may be increased following a subsequent dose of tetanus toxoid-containing vaccine, including BOOSTRIX. (5.2)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including BOOSTRIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.3)
- Progressive or unstable neurologic conditions are reasons to defer vaccination with a pertussis-containing vaccine, including BOOSTRIX. (5.4)

- Persons who experienced an Arthus-type hypersensitivity reaction following a prior dose of a tetanus toxoid-containing vaccine should not receive BOOSTRIX unless at least 10 years have elapsed since the last dose of a tetanus toxoid-containing vaccine. (5.5)

**ADVERSE REACTIONS**

- Common solicited adverse events ( $\geq 15\%$ ) in adolescents (10 to 18 years of age) were pain, redness, and swelling at the injection site, increase in arm circumference of injected arm, headache, fatigue, and gastrointestinal symptoms. (6.1)
- Common solicited adverse events ( $\geq 15\%$ ) in adults (19 to 64 years of age) were pain, redness, and swelling at the injection site, headache, fatigue, and gastrointestinal symptoms. (6.1)
- The most common solicited adverse event ( $\geq 15\%$ ) in the elderly (65 years of age and older) was pain at the injection site. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

**DRUG INTERACTIONS**

- In subjects 11 to 18 years of age, lower levels for antibodies to pertactin were observed when BOOSTRIX was administered concomitantly with meningococcal conjugate vaccine (serogroups A, C, Y, and W-135) as compared with BOOSTRIX administered first. (7.1)
- In subjects 19 to 64 years of age, lower levels for antibodies to FHA and pertactin were observed when BOOSTRIX was administered concomitantly with an inactivated influenza vaccine as compared with BOOSTRIX alone. (7.1)
- Do not mix BOOSTRIX with any other vaccine in the same syringe or vial. (7.1)

**USE IN SPECIFIC POPULATIONS**

- Safety and effectiveness of BOOSTRIX have not been established in pregnant women. (8.1)
- Register women who receive BOOSTRIX while pregnant in the pregnancy registry by calling 1-888-452-9622. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: xx/xxxx

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\*Sections or subsections omitted from the full prescribing information are not listed.

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

BOOSTRIX<sup>®</sup> is indicated for active booster immunization against tetanus, diphtheria, and pertussis. BOOSTRIX is approved for use as a single dose in individuals 10 years of age and older.

### **2 DOSAGE AND ADMINISTRATION**

#### **2.1 Preparation for Administration**

Shake vigorously to obtain a homogeneous, turbid, white suspension before administration. Do not use if resuspension does not occur with vigorous shaking. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

For the prefilled syringes, attach a sterile needle and administer intramuscularly.

For the vials, use a sterile needle and sterile syringe to withdraw the 0.5-mL dose and administer intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. Use a separate sterile needle and syringe for each individual.

Do not administer this product intravenously, intradermally, or subcutaneously.

#### **2.2 Dose and Schedule**

BOOSTRIX is administered as a single 0.5-mL intramuscular injection into the deltoid muscle of the upper arm.

There are no data to support repeat administration of BOOSTRIX.

Five years should elapse between the last dose of the recommended series of Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and/or Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) vaccine and the administration of BOOSTRIX.

#### **2.3 Additional Dosing Information**

##### **Primary Series**

The use of BOOSTRIX as a primary series or to complete the primary series for diphtheria, tetanus, or pertussis has not been studied.

## Wound Management

If tetanus prophylaxis is needed for wound management, BOOSTRIX may be given if no previous dose of any Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap) has been administered.

## **3 DOSAGE FORMS AND STRENGTHS**

BOOSTRIX is a suspension for injection available in 0.5-mL single-dose vials and prefilled TIP-LOK<sup>®</sup> syringes.

## **4 CONTRAINDICATIONS**

### **4.1 Hypersensitivity**

A severe allergic reaction (e.g., anaphylaxis) after a previous dose of any tetanus toxoid-, diphtheria toxoid-, or pertussis antigen-containing vaccine or any component of this vaccine is a contraindication to administration of BOOSTRIX [*see Description (11)*]. Because of the uncertainty as to which component of the vaccine might be responsible, none of the components should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if immunization with any of these components is considered.

### **4.2 Encephalopathy**

Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis antigen-containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of any pertussis antigen-containing vaccine, including BOOSTRIX.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Latex**

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

### **5.2 Guillain-Barré Syndrome and Brachial Neuritis**

If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk of Guillain-Barré syndrome may be increased following a subsequent dose of tetanus toxoid-containing vaccine, including BOOSTRIX. A review by the Institute of Medicine (IOM) found evidence for a causal relationship between receipt of tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome.<sup>1</sup>

### **5.3 Syncope**

Syncope (fainting) can occur in association with administration of injectable vaccines, including BOOSTRIX. Syncope can be accompanied by transient neurological signs such as visual



disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

#### **5.4 Progressive or Unstable Neurologic Disorders**

Progressive or unstable neurologic conditions (e.g., cerebrovascular events and acute encephalopathic conditions) are reasons to defer vaccination with a pertussis-containing vaccine, including BOOSTRIX. It is not known whether administration of BOOSTRIX to persons with an unstable or progressive neurologic disorder might hasten manifestations of the disorder or affect the prognosis. Administration of BOOSTRIX to persons with an unstable or progressive neurologic disorder may result in diagnostic confusion between manifestations of the underlying illness and possible adverse effects of vaccination.

#### **5.5 Arthus-Type Hypersensitivity**

Persons who experienced an Arthus-type hypersensitivity reaction following a prior dose of a tetanus toxoid-containing vaccine usually have a high serum tetanus antitoxin level and should not receive BOOSTRIX or other tetanus toxoid-containing vaccines unless at least 10 years have elapsed since the last dose of tetanus toxoid-containing vaccine.

#### **5.6 Altered Immunocompetence**

As with any vaccine, if administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

#### **5.7 Prevention and Management of Acute Allergic Reactions**

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

### **6 ADVERSE REACTIONS**

#### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. As with any vaccine, there is the possibility that broad use of BOOSTRIX could reveal adverse reactions not observed in clinical trials.

In clinical studies, 4,949 adolescents (10 to 18 years of age) and 4,076 adults (19 years of age and older) were vaccinated with a single dose of BOOSTRIX. Of these adolescents, 1,341 were vaccinated with BOOSTRIX in a coadministration study with meningococcal conjugate vaccine [see *Drug Interactions (7.1)*, *Clinical Studies (14.5)*]. Of these adults, 1,104 were 65 years of age

99 and older [see *Clinical Studies (14.4)*]. A total of 860 adults 19 years of age and older received  
 100 concomitant vaccination with BOOSTRIX and influenza vaccines in a coadministration study  
 101 [see *Drug Interactions (7.1)*, *Clinical Studies (14.5)*]. An additional 1,092 adolescents 10 to  
 102 18 years of age received a non-US formulation of BOOSTRIX (formulated to contain 0.5 mg  
 103 aluminum per dose) in non-US clinical studies.

104 In a randomized, observer-blinded, controlled study in the US, 3,080 adolescents 10 to 18 years  
 105 of age received a single dose of BOOSTRIX and 1,034 received the comparator Td vaccine,  
 106 manufactured by MassBioLogics. There were no substantive differences in demographic  
 107 characteristics between the vaccine groups. Among BOOSTRIX and comparator vaccine  
 108 recipients, approximately 75% were 10 to 14 years of age and approximately 25% were 15 to  
 109 18 years of age. Approximately 98% of participants in this study had received the recommended  
 110 series of 4 or 5 doses of either Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed  
 111 (DTwP) or a combination of DTwP and DTaP in childhood. Subjects were monitored for  
 112 solicited adverse events using standardized diary cards (Day 0-14). Unsolicited adverse events  
 113 were monitored for the 31-day period following vaccination (Day 0-30). Subjects were also  
 114 monitored for 6 months post-vaccination for non-routine medical visits, visits to an emergency  
 115 room, onset of new chronic illness, and serious adverse events. Information regarding late onset  
 116 adverse events was obtained via a telephone call 6 months following vaccination. At least 97%  
 117 of subjects completed the 6-month follow-up evaluation.

118 In a study conducted in Germany, BOOSTRIX was administered to 319 children 10 to 12 years  
 119 of age previously vaccinated with 5 doses of acellular pertussis antigen-containing vaccines; 193  
 120 of these subjects had previously received 5 doses of INFANRIX<sup>®</sup> (Diphtheria and Tetanus  
 121 Toxoids and Acellular Pertussis Vaccine Adsorbed). Adverse events were recorded on diary  
 122 cards during the 15 days following vaccination. Unsolicited adverse events that occurred within  
 123 31 days of vaccination (Day 0-30) were recorded on the diary card or verbally reported to the  
 124 investigator. Subjects were monitored for 6 months post-vaccination for physician office visits,  
 125 emergency room visits, onset of new chronic illness, and serious adverse events. The 6-month  
 126 follow-up evaluation, conducted via telephone interview, was completed by 90% of subjects.

127 The US adult (19 to 64 years of age) study, a randomized, observer-blinded study, evaluated the  
 128 safety of BOOSTRIX (N = 1,522) compared with ADACEL<sup>®</sup> (Tetanus Toxoid, Reduced  
 129 Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed) (N = 762), a Tdap vaccine  
 130 manufactured by Sanofi Pasteur SA. Vaccines were administered as a single dose. There were no  
 131 substantive differences in demographic characteristics between the vaccine groups. Subjects  
 132 were monitored for solicited adverse events using standardized diary cards (Day 0-14).  
 133 Unsolicited adverse events were monitored for the 31-day period following vaccination (Day 0-  
 134 30). Subjects were also monitored for 6 months post-vaccination for serious adverse events,  
 135 visits to an emergency room, hospitalizations, and onset of new chronic illness. Approximately  
 136 95% of subjects completed the 6-month follow-up evaluation.

137 The US elderly (65 years of age and older) study, a randomized, observer-blinded study,

138 evaluated the safety of BOOSTRIX (N = 887) compared with DECAVAC<sup>®</sup> (Tetanus and  
139 Diphtheria Toxoids Adsorbed) (N = 445), a US-licensed Td vaccine, manufactured by Sanofi  
140 Pasteur SA. Vaccines were administered as a single dose. Among all vaccine recipients, the  
141 mean age was approximately 72 years; 54% were female and 95% were white. Subjects were  
142 monitored for solicited adverse events using standardized diary cards (Day 0-3). Unsolicited  
143 adverse events were monitored for the 31-day period following vaccination (Day 0-30). Subjects  
144 were also monitored for 6 months post-vaccination for serious adverse events. Approximately  
145 99% of subjects completed the 6-month follow-up evaluation.

146 Solicited Adverse Events in the US Adolescent Study

147 Table 1 presents the solicited local adverse reactions and general adverse events within 15 days  
148 of vaccination with BOOSTRIX or Td vaccine for the total vaccinated cohort.

149 The primary safety endpoint was the incidence of Grade 3 pain (spontaneously painful and/or  
150 prevented normal activity) at the injection site within 15 days of vaccination. Grade 3 pain was  
151 reported in 4.6% of those who received BOOSTRIX compared with 4.0% of those who received  
152 the Td vaccine. The difference in rate of Grade 3 pain was within the pre-defined clinical limit  
153 for non-inferiority (upper limit of the 95% CI for the difference [BOOSTRIX minus Td]  $\leq 4\%$ ).

154 **Table 1. Rates of Solicited Local Adverse Reactions or General Adverse Events within the 15-**  
 155 **Day<sup>a</sup> Post-vaccination Period in Adolescents 10 to 18 Years of Age (Total Vaccinated Cohort)**

	<b>BOOSTRIX</b> (N = 3,032) %	<b>Td</b> (N = 1,013) %
<b>Local</b>		
Pain, any <sup>b</sup>	75.3	71.7
Pain, Grade 2 or 3 <sup>b</sup>	51.2	42.5
Pain, Grade 3 <sup>c</sup>	4.6	4.0
Redness, any	22.5	19.8
Redness, >20 mm	4.1	3.9
Redness, ≥50 mm	1.7	1.6
Swelling, any	21.1	20.1
Swelling, >20 mm	5.3	4.9
Swelling, ≥50 mm	2.5	3.2
Arm circumference increase, >5 mm <sup>d</sup>	28.3	29.5
Arm circumference increase, >20 mm <sup>d</sup>	2.0	2.2
Arm circumference increase, >40 mm <sup>d</sup>	0.5	0.3
<b>General</b>		
Headache, any	43.1	41.5
Headache, Grade 2 or 3 <sup>b</sup>	15.7	12.7
Headache, Grade 3	3.7	2.7
Fatigue, any	37.0	36.7
Fatigue, Grade 2 or 3	14.4	12.9
Fatigue, Grade 3	3.7	3.2
Gastrointestinal symptoms, any <sup>e</sup>	26.0	25.8
Gastrointestinal symptoms, Grade 2 or 3 <sup>e</sup>	9.8	9.7
Gastrointestinal symptoms, Grade 3 <sup>e</sup>	3.0	3.2
Fever, ≥99.5°F (37.5°C) <sup>f</sup>	13.5	13.1
Fever, >100.4°F (38.0°C) <sup>f</sup>	5.0	4.7
Fever, >102.2°F (39.0°C) <sup>f</sup>	1.4	1.0

156 Td = Tetanus and Diphtheria Toxoids Adsorbed For Adult Use manufactured by MassBioLogics.

157 N = Number of subjects in the total vaccinated cohort with local/general symptoms sheets

158 completed.

159 Grade 2 = Local: painful when limb moved; General: interfered with normal activity.

160 Grade 3 = Local: spontaneously painful and/or prevented normal activity; General: prevented  
 161 normal activity.

162 <sup>a</sup> Day of vaccination and the next 14 days.

163 <sup>b</sup> Statistically significantly higher ( $P < 0.05$ ) following BOOSTRIX as compared with Td  
 164 vaccine.

165 <sup>c</sup> Grade 3 injection site pain following BOOSTRIX was not inferior to Td vaccine (upper limit of  
 166 two-sided 95% CI for the difference [BOOSTRIX minus Td] in the percentage of subjects ≤4%).

167 <sup>d</sup> Mid-upper region of the vaccinated arm.

168 <sup>e</sup> Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

169 <sup>f</sup> Oral temperatures or axillary temperatures.

170 **Unsolicited Adverse Events in the US Adolescent Study**

171 The incidence of unsolicited adverse events reported in the 31 days after vaccination was  
172 comparable between the 2 groups (25.4% and 24.5% for BOOSTRIX and Td vaccine,  
173 respectively).

174 **Solicited Adverse Events in the German Adolescent Study**

175 Table 2 presents the rates of solicited local adverse reactions and fever within 15 days of  
176 vaccination for those subjects who had previously been vaccinated with 5 doses of INFANRIX.  
177 No cases of whole arm swelling were reported. Two individuals (2/193) reported large injection  
178 site swelling (range: 110 to 200 mm diameter), in one case associated with Grade 3 pain. Neither  
179 individual sought medical attention. These episodes were reported to resolve without sequelae  
180 within 5 days.

181 **Table 2. Rates of Solicited Adverse Events Reported within the 15-Day<sup>a</sup> Post-vaccination**  
182 **Period following Administration of BOOSTRIX in Adolescents 10 to 12 Years of Age Who**  
183 **Had Previously Received 5 Doses of INFANRIX**

	<b>BOOSTRIX (N = 193) %</b>
Pain, any	62.2
Pain, Grade 2 or 3	33.2
Pain, Grade 3	5.7
Redness, any	47.7
Redness, >20 mm	15.0
Redness, ≥50 mm	10.9
Swelling, any	38.9
Swelling, >20 mm	17.6
Swelling, ≥50 mm	14.0
Fever, ≥99.5°F (37.5°C) <sup>b</sup>	8.8
Fever, >100.4°F (38.0°C) <sup>b</sup>	4.1
Fever, >102.2°F (39.0°C) <sup>b</sup>	1.0

184 N = Number of subjects with local/general symptoms sheets completed.

185 Grade 2 = Painful when limb moved.

186 Grade 3 = Spontaneously painful and/or prevented normal activity.

187 <sup>a</sup> Day of vaccination and the next 14 days.

188 <sup>b</sup> Oral temperatures or axillary temperatures.

189 **Solicited Adverse Events in the US Adult (19 to 64 Years of Age) Study**

190 Table 3 presents solicited local adverse reactions and general adverse events within 15 days of  
191 vaccination with BOOSTRIX or the comparator Tdap vaccine for the total vaccinated cohort.

**Table 3. Rates of Solicited Local Adverse Reactions or General Adverse Events within the 15-Day<sup>a</sup> Post-vaccination Period in Adults 19 to 64 Years of Age (Total Vaccinated Cohort)**

	<b>BOOSTRIX (N = 1,480) %</b>	<b>Tdap (N = 741) %</b>
<b>Local</b>		
Pain, any	61.0	69.2
Pain, Grade 2 or 3	35.1	44.4
Pain, Grade 3	1.6	2.3
Redness, any	21.1	27.1
Redness, >20 mm	4.0	6.2
Redness, ≥50 mm	1.6	2.3
Swelling, any	17.6	25.6
Swelling, >20 mm	3.9	6.3
Swelling, ≥50 mm	1.4	2.8
<b>General</b>		
Headache, any	30.1	31.0
Headache, Grade 2 or 3	11.1	10.5
Headache, Grade 3	2.2	1.5
Fatigue, any	28.1	28.9
Fatigue, Grade 2 or 3	9.1	9.4
Fatigue, Grade 3	2.5	1.2
Gastrointestinal symptoms, any <sup>b</sup>	15.9	17.5
Gastrointestinal symptoms, Grade 2 or 3 <sup>b</sup>	4.3	5.7
Gastrointestinal symptoms, Grade 3 <sup>b</sup>	1.2	1.3
Fever, ≥99.5°F (37.5°C) <sup>c</sup>	5.5	8.0
Fever, >100.4°F (38.0°C) <sup>c</sup>	1.0	1.5
Fever, >102.2°F (39.0°C) <sup>c</sup>	0.1	0.4

Tdap = Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed, a Tdap vaccine manufactured by Sanofi Pasteur SA.

N = Number of subjects in the total vaccinated cohort with local/general symptoms sheets completed.

Grade 2 = Local: painful when limb moved; General: interfered with normal activity.

Grade 3 = Local/General: prevented normal activity.

<sup>a</sup> Day of vaccination and the next 14 days.

<sup>b</sup> Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

<sup>c</sup> Oral temperatures.

### Unsolicited Adverse Events in the US Adult (19 to 64 Years of Age) Study

The incidence of unsolicited adverse events reported in the 31 days after vaccination was comparable between the 2 groups (17.8% and 22.2% for BOOSTRIX and Tdap vaccine, respectively).

207 Solicited Adverse Events in the US Elderly (65 Years of Age and Older) Study

208 Table 4 presents solicited local adverse reactions and general adverse events within 4 days of  
 209 vaccination with BOOSTRIX or the comparator Td vaccine for the total vaccinated cohort.

210 **Table 4. Rates of Solicited Local Adverse Reactions or General Adverse Events within**  
 211 **4 Days<sup>a</sup> of Vaccination in the Elderly 65 Years of Age and Older (Total Vaccinated Cohort)**

	<b>BOOSTRIX</b> %	<b>Td</b> %
<b>Local</b>	<b>(N = 882)</b>	<b>(N = 444)</b>
Pain, any	21.5	27.7
Pain, Grade 2 or 3	7.5	10.1
Pain, Grade 3	0.2	0.7
Redness, any	10.8	12.6
Redness, >20 mm	1.4	2.5
Redness, ≥50 mm	0.6	0.9
Swelling, any	7.5	11.7
Swelling, >20 mm	2.2	3.4
Swelling, ≥50 mm	0.7	0.7
<b>General</b>	<b>(N = 882)</b>	<b>(N = 445)</b>
Fatigue, any	12.5	14.8
Fatigue, Grade 2 or 3	2.5	2.9
Fatigue, Grade 3	0.7	0.7
Headache, any	11.5	11.7
Headache, Grade 2 or 3	1.9	2.2
Headache, Grade 3	0.6	0.0
Gastrointestinal symptoms, any <sup>b</sup>	7.6	9.2
Gastrointestinal symptoms, Grade 2 or 3 <sup>b</sup>	1.7	1.8
Gastrointestinal symptoms, Grade 3 <sup>b</sup>	0.3	0.4
Fever, ≥99.5°F (37.5°C) <sup>c</sup>	2.0	2.5
Fever, >100.4°F (38.0°C) <sup>c</sup>	0.2	0.2
Fever, >102.2°F (39.0°C) <sup>c</sup>	0.0	0.0

212 Td = Tetanus and Diphtheria Toxoids Adsorbed, a US-licensed Td vaccine, manufactured by  
 213 Sanofi Pasteur SA.

214 N = Number of subjects with a documented dose.

215 Grade 2 = Local: painful when limb moved; General: interfered with normal activity.

216 Grade 3 = Local/General: prevented normal activity.

217 <sup>a</sup> Day of vaccination and the next 3 days.

218 <sup>b</sup> Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

219 <sup>c</sup> Oral temperatures.

220 Unsolicited Adverse Events in the US Elderly (65 Years of Age and Older) Study

221 The incidence of unsolicited adverse events reported in the 31 days after vaccination was  
 222 comparable between the 2 groups (17.1% and 14.4% for BOOSTRIX and Td vaccine,



respectively).

#### Serious Adverse Events (SAEs)

In the US and German adolescent safety studies, no serious adverse events were reported to occur within 31 days of vaccination. During the 6-month extended safety evaluation period, no serious adverse events that were of potential autoimmune origin or new onset and chronic in nature were reported to occur. In non-US adolescent studies in which serious adverse events were monitored for up to 37 days, one subject was diagnosed with insulin-dependent diabetes 20 days following administration of BOOSTRIX. No other serious adverse events of potential autoimmune origin or that were new onset and chronic in nature were reported to occur in these studies. In the US adult (19 to 64 years of age) study, serious adverse events were reported to occur during the entire study period (0-6 months) by 1.4% and 1.7% of subjects who received BOOSTRIX and the comparator Tdap vaccine, respectively. During the 6-month extended safety evaluation period, no serious adverse events of a neuroinflammatory nature or with information suggesting an autoimmune etiology were reported in subjects who received BOOSTRIX. In the US elderly (65 years of age and older) study, serious adverse events were reported to occur by 0.7% and 0.9% of subjects who received BOOSTRIX and the comparator Td vaccine, respectively, during the 31-day period after vaccination. Serious adverse events were reported to occur by 4.2% and 2.2% of subjects who received BOOSTRIX and the comparator Td vaccine, respectively, during the 6-month period after vaccination.

#### Concomitant Vaccination with Meningococcal Conjugate Vaccine in Adolescents

In a randomized study in the US, 1,341 adolescents (11 to 18 years of age) received either BOOSTRIX administered concomitantly with MENACTRA<sup>®</sup> (Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine), (Sanofi Pasteur SA), or each vaccine administered separately 1 month apart [*see Drug Interactions (7.1), Clinical Studies (14.5)*]. Safety was evaluated in 446 subjects who received BOOSTRIX administered concomitantly with meningococcal conjugate vaccine at different injection sites, 446 subjects who received BOOSTRIX followed by meningococcal conjugate vaccine 1 month later, and 449 subjects who received meningococcal conjugate vaccine followed by BOOSTRIX 1 month later. Solicited local adverse reactions and general adverse events were recorded on diary cards for 4 days (Day 0-3) following each vaccination. Unsolicited adverse events were monitored for the 31-day period following each vaccination (Day 0-30). Table 5 presents the percentages of subjects experiencing local reactions at the injection site for BOOSTRIX and solicited general events following BOOSTRIX. The incidence of unsolicited adverse events reported in the 31 days after any vaccination was similar following each dose of BOOSTRIX in all cohorts.



**Table 5. Rates of Solicited Local Adverse Reactions or General Adverse Events Reported within the 4-Day Post-vaccination Period following Administration of BOOSTRIX in Individuals 11 to 18 Years of Age (Total Vaccinated Cohort)**

	<b>BOOSTRIX+MCV4<sup>a</sup></b> (N = 441) %	<b>BOOSTRIX→MCV4<sup>b</sup></b> (N = 432-433) %	<b>MCV4→BOOSTRIX<sup>c</sup></b> (N = 441) %
<b>Local (at injection site for BOOSTRIX)</b>			
Pain, any	70.1	70.4	47.8
Redness, any	22.7	25.7	17.9
Swelling, any	17.7	18.1	12.0
<b>General (following administration of BOOSTRIX)</b>			
Fatigue	34.0	32.1	20.4
Headache	34.0	30.7	17.0
Gastrointestinal symptoms <sup>d</sup>	15.2	14.5	7.7
Fever, ≥99.5°F (37.5°C) <sup>e</sup>	5.2	3.5	2.3

MCV4 = MENACTRA (Meningococcal (Groups A, C, Y, and W-135) Polysaccharide

Diphtheria Toxoid Conjugate Vaccine), Sanofi Pasteur SA.

N = number of subjects in the total vaccinated cohort with local/general symptoms sheets completed.

<sup>a</sup> BOOSTRIX+MCV4 = Concomitant vaccination with BOOSTRIX and MENACTRA.

<sup>b</sup> BOOSTRIX→MCV4 = BOOSTRIX followed by MCV4 1 month later.

<sup>c</sup> MCV4→BOOSTRIX = MCV4 followed by BOOSTRIX 1 month later.

<sup>d</sup> Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

<sup>e</sup> Oral temperatures.

## **6.2 Postmarketing Experience**

In addition to reports in clinical trials, worldwide voluntary reports of adverse events received for BOOSTRIX in persons 10 years of age and older since market introduction of this vaccine are listed below. This list includes serious events or events that have causal connection to components of this or other vaccines or drugs. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

### Blood and Lymphatic System Disorders

Lymphadenitis, lymphadenopathy.

### Immune System Disorders

Allergic reactions, including anaphylactic and anaphylactoid reactions.

Cardiac Disorders

Myocarditis.

General Disorders and Administration Site Conditions

Extensive swelling of the injected limb, injection site induration, injection site inflammation, injection site mass, injection site pruritus, injection site nodule, injection site warmth, injection site reaction.

Musculoskeletal and Connective Tissue Disorders

Arthralgia, back pain, myalgia.

Nervous System Disorders

Convulsions (with and without fever), encephalitis, facial palsy, loss of consciousness, paraesthesia, syncope.

Skin and Subcutaneous Tissue Disorders

Angioedema, exanthem, Henoch-Schönlein purpura, rash, urticaria.

**7 DRUG INTERACTIONS**

**7.1 Concomitant Vaccine Administration**

BOOSTRIX was administered concomitantly with MENACTRA in a clinical study of subjects 11 to 18 years of age [see *Clinical Studies (14.5)*]. Post-vaccination geometric mean antibody concentrations (GMCs) to pertactin were lower following BOOSTRIX administered concomitantly with meningococcal conjugate vaccine compared with BOOSTRIX administered first. It is not known if the efficacy of BOOSTRIX is affected by the reduced response to pertactin.

BOOSTRIX was administered concomitantly with FLUARIX<sup>®</sup> (Influenza Virus Vaccine) in a clinical study of subjects 19 to 64 years of age [see *Clinical Studies (14.5)*]. Lower GMCs for antibodies to the pertussis antigens filamentous hemagglutinin (FHA) and pertactin were observed when BOOSTRIX was administered concomitantly with FLUARIX as compared with BOOSTRIX alone. It is not known if the efficacy of BOOSTRIX is affected by the reduced response to FHA and pertactin.

When BOOSTRIX is administered concomitantly with other injectable vaccines or Tetanus Immune Globulin, they should be given with separate syringes and at different injection sites. BOOSTRIX should not be mixed with any other vaccine in the same syringe or vial.

**7.2 Immunosuppressive Therapies**

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to BOOSTRIX.

## **USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### **Pregnancy Category B**

A developmental toxicity study has been performed in female rats at a dose approximately 40 times the human dose (on a mL/kg basis) and revealed no evidence of harm to the fetus due to BOOSTRIX. Animal fertility studies have not been conducted with BOOSTRIX. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, BOOSTRIX should be given to a pregnant woman only if clearly needed.

In a developmental toxicity study, the effect of BOOSTRIX on embryo-fetal and pre-weaning development was evaluated in pregnant rats. Animals were administered INFANRIX by intramuscular injection once prior to gestation and BOOSTRIX by intramuscular injection during the period of organogenesis (gestation Days 6, 8, 11, and 15), 0.1 mL/rat/occasion (approximately 40-fold excess relative to the projected human dose of BOOSTRIX on a body weight basis). The antigens in INFANRIX are the same as those in BOOSTRIX, but INFANRIX is formulated with higher quantities of these antigens. No adverse effects on pregnancy, parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

#### **Pregnancy Registry**

GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with BOOSTRIX during pregnancy. Women who receive BOOSTRIX during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-888-452-9622.

### **8.3 Nursing Mothers**

It is not known whether BOOSTRIX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOOSTRIX is administered to a nursing woman.

### **8.4 Pediatric Use**

BOOSTRIX is not indicated for use in children younger than 10 years of age. Safety and effectiveness of BOOSTRIX in this age group have not been established.

### **8.5 Geriatric Use**

In clinical trials, 1,104 subjects 65 years of age and older received BOOSTRIX; of these subjects, 299 were 75 years of age and older. In the US elderly (65 years and older) study, immune responses to tetanus and diphtheria toxoids following BOOSTRIX were non-inferior to the comparator Td vaccine. Antibody responses to pertussis antigens following a single dose of

BOOSTRIX in the elderly were non-inferior to those observed with INFANRIX administered as a 3-dose series in infants [see *Clinical Studies (14.4)*]. Solicited adverse events following BOOSTRIX were similar in frequency to those reported with the comparator Td vaccine [see *Adverse Reactions (6.1)*].

## 11 DESCRIPTION

BOOSTRIX (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed) is a noninfectious, sterile, vaccine for intramuscular administration. It contains tetanus toxoid, diphtheria toxoid, and pertussis antigens (inactivated pertussis toxin [PT] and formaldehyde-treated filamentous hemagglutinin [FHA] and pertactin). The antigens are the same as those in INFANRIX, but BOOSTRIX is formulated with reduced quantities of these antigens.

Tetanus toxin is produced by growing *Clostridium tetani* in a modified Latham medium derived from bovine casein. The diphtheria toxin is produced by growing *Corynebacterium diphtheriae* in Fenton medium containing a bovine extract. The bovine materials used in these extracts are sourced from countries which the United States Department of Agriculture (USDA) has determined neither have nor are at risk of bovine spongiform encephalopathy (BSE). Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and purified by precipitation, dialysis, and sterile filtration.

The acellular pertussis antigens (PT, FHA, and pertactin) are isolated from *Bordetella pertussis* culture grown in modified Stainer-Scholte liquid medium. PT and FHA are isolated from the fermentation broth; pertactin is extracted from the cells by heat treatment and flocculation. The antigens are purified in successive chromatographic and precipitation steps. PT is detoxified using glutaraldehyde and formaldehyde. FHA and pertactin are treated with formaldehyde.

Each antigen is individually adsorbed onto aluminum hydroxide. Each 0.5-mL dose is formulated to contain 5 Lf of tetanus toxoid, 2.5 Lf of diphtheria toxoid, 8 mcg of inactivated PT, 8 mcg of FHA, and 2.5 mcg of pertactin (69 kiloDalton outer membrane protein).

Tetanus and diphtheria toxoid potency is determined by measuring the amount of neutralizing antitoxin in previously immunized guinea pigs. The potency of the acellular pertussis components (inactivated PT and formaldehyde-treated FHA and pertactin) is determined by enzyme-linked immunosorbent assay (ELISA) on sera from previously immunized mice.

Each 0.5-mL dose contains aluminum hydroxide as adjuvant (not more than 0.39 mg aluminum by assay), 4.5 mg of sodium chloride,  $\leq 100$  mcg of residual formaldehyde, and  $\leq 100$  mcg of polysorbate 80 (Tween 80).

BOOSTRIX is available in vials and prefilled syringes. The tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with natural rubber latex. The vial stoppers are not made with natural rubber latex.

BOOSTRIX is formulated without preservatives.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

#### **Tetanus**

Tetanus is a condition manifested primarily by neuromuscular dysfunction caused by a potent exotoxin released by *C. tetani*. Protection against disease is due to the development of neutralizing antibodies to the tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assays, is considered the minimum protective level.<sup>2</sup> A level  $\geq 0.1$  IU/mL by ELISA has been considered as protective.

#### **Diphtheria**

Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL, measured by neutralization assays, is the lowest level giving some degree of protection; a level of 0.1 IU/mL by ELISA is regarded as protective.<sup>3</sup> Diphtheria antitoxin levels  $\geq 1.0$  IU/mL by ELISA have been associated with long-term protection.<sup>3</sup>

#### **Pertussis**

Pertussis (whooping cough) is a disease of the respiratory tract caused by *B. pertussis*. The role of the different components produced by *B. pertussis* in either the pathogenesis of, or the immunity to, pertussis is not well understood.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

BOOSTRIX has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

## **14 CLINICAL STUDIES**

The efficacy of the tetanus and diphtheria toxoid components of BOOSTRIX is based on the immunogenicity of the individual antigens compared with US-licensed vaccines using established serologic correlates of protection. The efficacy of the pertussis components of BOOSTRIX was evaluated by comparison of the immune response of adolescents and adults following a single dose of BOOSTRIX to the immune response of infants following a 3-dose primary series of INFANRIX. In addition, the ability of BOOSTRIX to induce a booster response to each of the antigens was evaluated.

## 14.1 Efficacy of INFANRIX

The efficacy of a 3-dose primary series of INFANRIX in infants has been assessed in 2 clinical studies: A prospective efficacy trial conducted in Germany employing a household contact study design and a double-blind, randomized, active Diphtheria and Tetanus Toxoids (DT)-controlled trial conducted in Italy sponsored by the National Institutes of Health (NIH) (for details see INFANRIX prescribing information). Serological data from a subset of infants immunized with INFANRIX in the household contact study were compared with the sera of adolescents and adults immunized with BOOSTRIX [see *Clinical Studies (14.2, 14.3)*]. In the household contact study, the protective efficacy of INFANRIX, in infants, against WHO-defined pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing) was calculated to be 89% (95% CI: 77%, 95%). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX against  $\geq 7$  days of any cough was 67% (95% CI: 52%, 78%) and against  $\geq 7$  days of paroxysmal cough was 81% (95% CI: 68%, 89%) (for details see INFANRIX prescribing information).

## 14.2 Immunological Evaluation in Adolescents

In a multicenter, randomized, controlled study conducted in the United States, the immune responses to each of the antigens contained in BOOSTRIX were evaluated in sera obtained approximately 1 month after administration of a single dose of vaccine to adolescent subjects (10 to 18 years of age). Of the subjects enrolled in this study, approximately 76% were 10 to 14 years of age and 24% were 15 to 18 years of age. Approximately 98% of participants in this study had received the recommended series of 4 or 5 doses of either DTwP or a combination of DTwP and DTaP in childhood. The racial/ethnic demographics were as follows: white 85.8%, black 5.7%, Hispanic 5.6%, Oriental 0.8%, and other 2.1%.

### Response to Tetanus and Diphtheria Toxoids

The antibody responses to the tetanus and diphtheria toxoids of BOOSTRIX compared with Td vaccine are shown in Table 6. One month after a single dose, anti-tetanus and anti-diphtheria seroprotective rates ( $\geq 0.1$  IU/mL by ELISA) and booster response rates were comparable between BOOSTRIX and the comparator Td vaccine.

**Table 6. Antibody Responses to Tetanus and Diphtheria Toxoids following BOOSTRIX Compared with Td Vaccine in Adolescents 10 to 18 Years of Age (ATP Cohort for Immunogenicity)**

	N	% $\geq 0.1$ IU/mL <sup>a</sup> (95% CI)	% $\geq 1.0$ IU/mL <sup>a</sup> (95% CI)	% Booster Response <sup>b</sup> (95% CI)
<b>Anti-tetanus</b>				
BOOSTRIX	2,469-2,516			
Pre-vaccination		97.7 (97.1, 98.3)	36.8 (34.9, 38.7)	–
Post-vaccination		100 (99.8, 100) <sup>c</sup>	99.5 (99.1, 99.7) <sup>d</sup>	89.7 (88.4, 90.8) <sup>c</sup>
Td	817-834			
Pre-vaccination		96.8 (95.4, 97.9)	39.9 (36.5, 43.4)	–
Post-vaccination		100 (99.6, 100)	99.8 (99.1, 100)	92.5 (90.5, 94.2)
<b>Anti-diphtheria</b>				
BOOSTRIX	2,463-2,515			
Pre-vaccination		85.8 (84.3, 87.1)	17.1 (15.6, 18.6)	–
Post-vaccination		99.9 (99.7, 100) <sup>c</sup>	97.3 (96.6, 97.9) <sup>d</sup>	90.6 (89.4, 91.7) <sup>c</sup>
Td	814-834			
Pre-vaccination		84.8 (82.1, 87.2)	19.5 (16.9, 22.4)	–
Post-vaccination		99.9 (99.3, 100)	99.3 (98.4, 99.7)	95.9 (94.4, 97.2)

Td manufactured by MassBioLogics.

ATP = According-to-protocol; CI = Confidence Interval.

<sup>a</sup> Measured by ELISA.

<sup>b</sup> Booster response: In subjects with pre-vaccination  $< 0.1$  IU/mL, post-vaccination concentration  $\geq 0.4$  IU/mL. In subjects with pre-vaccination concentration  $\geq 0.1$  IU/mL, an increase of at least 4 times the pre-vaccination concentration.

<sup>c</sup> Seroprotection rate or booster response rate to BOOSTRIX was non-inferior to Td (upper limit of two-sided 95% CI on the difference for Td minus BOOSTRIX  $\leq 10\%$ ).

<sup>d</sup> Non-inferiority criteria not prospectively defined for this endpoint.

#### Response to Pertussis Antigens

The booster response rates of adolescents to the pertussis antigens are shown in Table 7. For each of the pertussis antigens the lower limit of the two-sided 95% CI for the percentage of subjects with a booster response exceeded the pre-defined lower limit of 80% for demonstration of an acceptable booster response.



**Table 7. Booster Responses to the Pertussis Antigens following BOOSTRIX in Adolescents 10 to 18 Years of Age (ATP Cohort for Immunogenicity)**

	N	BOOSTRIX % Booster Response <sup>a</sup> (95% CI)
Anti-PT	2,677	84.5 (83.0, 85.9)
Anti-FHA	2,744	95.1 (94.2, 95.9)
Anti-pertactin	2,752	95.4 (94.5, 96.1)

ATP = According-to-protocol; CI = Confidence Interval.

<sup>a</sup> Booster response: In initially seronegative subjects (<5 EL.U./mL), post-vaccination antibody concentrations  $\geq 20$  EL.U./mL. In initially seropositive subjects with pre-vaccination antibody concentrations  $\geq 5$  EL.U./mL and <20 EL.U./mL, an increase of at least 4 times the pre-vaccination antibody concentration. In initially seropositive subjects with pre-vaccination antibody concentrations  $\geq 20$  EL.U./mL, an increase of at least 2 times the pre-vaccination antibody concentration.

The GMCs to each of the pertussis antigens 1 month following a single dose of BOOSTRIX in the US adolescent study (N = 2,941 to 2,979) were compared with the GMCs observed in infants following a 3-dose primary series of INFANRIX administered at 3, 4, and 5 months of age (N = 631 to 2,884). Table 8 presents the results for the total immunogenicity cohort in both studies (vaccinated subjects with serology data available for at least one pertussis antigen; the majority of subjects in the study of INFANRIX had anti-PT serology data only). These infants were a subset of those who formed the cohort for the German household contact study in which the efficacy of INFANRIX was demonstrated [see *Clinical Studies (14.1)*]. Although a serologic correlate of protection for pertussis has not been established, anti-PT, anti-FHA, and anti-pertactin antibody concentrations observed in adolescents 1 month after a single dose of BOOSTRIX were non-inferior to those observed in infants following a primary vaccination series with INFANRIX.

**Table 8. Ratio of GMCs to Pertussis Antigens following One Dose of BOOSTRIX in Adolescents 10 to 18 Years of Age Compared with 3 Doses of INFANRIX in Infants (Total Immunogenicity Cohort)**

	GMC Ratio: BOOSTRIX/INFANRIX (95% CI)
Anti-PT	1.90 (1.82, 1.99) <sup>a</sup>
Anti-FHA	7.35 (6.85, 7.89) <sup>a</sup>
Anti-pertactin	4.19 (3.73, 4.71) <sup>a</sup>

GMC = Geometric mean antibody concentration, measured in ELISA units; CI = Confidence Interval.

Number of subjects for BOOSTRIX GMC evaluation: Anti-PT = 2,941, anti-FHA = 2,979, and anti-pertactin = 2,978.

Number of subjects for INFANRIX GMC evaluation: Anti-PT = 2,884, anti-FHA = 685, and



anti-pertactin = 631.

<sup>a</sup> GMC following BOOSTRIX was non-inferior to GMC following INFANRIX (lower limit of 95% CI for the GMC ratio of BOOSTRIX/INFANRIX >0.67).

### 14.3 Immunological Evaluation in Adults (19 to 64 Years of Age)

A multicenter, randomized, observer-blinded study, conducted in the United States, evaluated the immunogenicity of BOOSTRIX compared with the licensed comparator Tdap vaccine (Sanofi Pasteur SA). Vaccines were administered as a single dose to subjects (N = 2,284) who had not received a tetanus-diphtheria booster within 5 years. The immune responses to each of the antigens contained in BOOSTRIX were evaluated in sera obtained approximately 1 month after administration. Approximately 33% of patients were 19 to 29 years of age, 33% were 30 to 49 years of age and 34% were 50 to 64 years of age. Among subjects in the combined vaccine groups, 62% were female; 84% of subjects were white, 8% black, 1% Asian, and 7% were of other racial/ethnic groups.

#### Response to Tetanus and Diphtheria Toxoids

The antibody responses to the tetanus and diphtheria toxoids of BOOSTRIX compared with the comparator Tdap vaccine are shown in Table 9. One month after a single dose, anti-tetanus and anti-diphtheria seroprotective rates ( $\geq 0.1$  IU/mL by ELISA) were comparable between BOOSTRIX and the comparator Tdap vaccine.

**Table 9. Antibody Responses to Tetanus and Diphtheria Toxoids following One Dose of BOOSTRIX Compared with the Comparator Tdap Vaccine in Adults 19 to 64 Years of Age (ATP Cohort for Immunogenicity)**

	N	% $\geq 0.1$ IU/mL <sup>a</sup> (95% CI)	% $\geq 1.0$ IU/mL <sup>a</sup> (95% CI)
<b>Anti-tetanus</b>			
BOOSTRIX	1,445-1,447		
Pre-vaccination		95.9 (94.8, 96.9)	71.9 (69.5, 74.2)
Post-vaccination		99.6 (99.1, 99.8) <sup>b</sup>	98.3 (97.5, 98.9) <sup>b</sup>
Tdap	727-728		
Pre-vaccination		97.2 (95.8, 98.3)	74.7 (71.4, 77.8)
Post-vaccination		100 (95.5, 100)	99.3 (98.4, 99.8)
<b>Anti-diphtheria</b>			
BOOSTRIX	1,440-1,444		
Pre-vaccination		85.2 (83.3, 87.0)	23.7 (21.5, 26.0)
Post-vaccination		98.2 (97.4, 98.8) <sup>b</sup>	87.9 (86.1, 89.5) <sup>c</sup>
Tdap	720-727		
Pre-vaccination		89.2 (86.7, 91.3)	26.5 (23.3, 29.9)
Post-vaccination		98.6 (97.5, 99.3)	92.0 (89.8, 93.9)

Tdap = Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed

manufactured by Sanofi Pasteur SA.

ATP = According-to-protocol; CI = Confidence Interval.

<sup>a</sup> Measured by ELISA.

<sup>b</sup> Seroprotection rates for BOOSTRIX were non-inferior to the comparator Tdap vaccine (lower limit of 95% CI on the difference of BOOSTRIX minus Tdap  $\geq$  -10%).

<sup>c</sup> Non-inferiority criteria not prospectively defined for this endpoint.

### Response to Pertussis Antigens

Booster response rates to the pertussis antigens are shown in Table 10. For the FHA and pertactin antigens, the lower limit of the 95% CI for the booster responses exceeded the pre-defined limit of 80% demonstrating an acceptable booster response following BOOSTRIX. The PT antigen booster response lower limit of the 95% CI (74.9%) did not exceed the pre-defined limit of 80%.

**Table 10. Booster Responses to the Pertussis Antigens following One Dose of BOOSTRIX in Adults 19 to 64 Years of Age (ATP Cohort for Immunogenicity)**

	N	<b>BOOSTRIX</b> <b>% Booster Response<sup>a</sup></b> <b>(95% CI)</b>
Anti-PT	1,419	77.2 (74.9, 79.3) <sup>b</sup>
Anti-FHA	1,433	96.9 (95.8, 97.7) <sup>c</sup>
Anti-pertactin	1,441	93.2 (91.8, 94.4) <sup>c</sup>

ATP = According-to-protocol; CI = Confidence Interval.

<sup>a</sup> Booster response: In initially seronegative subjects ( $<5$  EL.U./mL), post-vaccination antibody concentrations  $\geq 20$  EL.U./mL. In initially seropositive subjects with pre-vaccination antibody concentrations  $\geq 5$  EL.U./mL and  $<20$  EL.U./mL, an increase of at least 4 times the pre-vaccination antibody concentration. In initially seropositive subjects with pre-vaccination antibody concentrations  $\geq 20$  EL.U./mL, an increase of at least 2 times the pre-vaccination antibody concentration.

<sup>b</sup> The PT antigen booster response lower limit of the 95% CI did not exceed the pre-defined limit of 80%.

<sup>c</sup> The FHA and pertactin antigens booster response lower limit of the 95% CI exceeded the pre-defined limit of 80%.

The GMCs to each of the pertussis antigens 1 month following a single dose of BOOSTRIX in the US adult (19 to 64 years of age) study were compared with the GMCs observed in infants following a 3-dose primary series of INFANRIX administered at 3, 4, and 5 months of age. Table 11 presents the results for the total immunogenicity cohort in both studies (vaccinated subjects with serology data available for at least one pertussis antigen). These infants were a subset of those who formed the cohort for the German household contact study in which the efficacy of INFANRIX was demonstrated [see *Clinical Studies (14.1)*]. Although a serologic

correlate of protection for pertussis has not been established, anti-PT, anti-FHA, and anti-pertactin antibody concentrations observed in adults 1 month after a single dose of BOOSTRIX were non-inferior to those observed in infants following a primary vaccination series with INFANRIX.

**Table 11. Ratio of GMCs to Pertussis Antigens following One Dose of BOOSTRIX in Adults 19 to 64 Years of Age Compared with 3 Doses of INFANRIX in Infants (Total Immunogenicity Cohort)**

	<b>GMC Ratio: BOOSTRIX/INFANRIX (95% CI)</b>
Anti-PT	1.39 (1.32, 1.47) <sup>a</sup>
Anti-FHA	7.46 (6.86, 8.12) <sup>a</sup>
Anti-pertactin	3.56 (3.10, 4.08) <sup>a</sup>

GMC = Geometric mean antibody concentration; CI = Confidence Interval.

Number of subjects for BOOSTRIX GMC evaluation: Anti-PT = 1,460, anti-FHA = 1,472, and anti-pertactin = 1,473.

Number of subjects for INFANRIX GMC evaluation: Anti-PT = 2,884, anti-FHA = 685, and anti-pertactin = 631.

<sup>a</sup> BOOSTRIX was non-inferior to INFANRIX (lower limit of 95% CI for the GMC ratio of BOOSTRIX/INFANRIX  $\geq 0.67$ ).

#### **14.4 Immunological Evaluation in the Elderly (65 Years of Age and Older)**

The US elderly (65 years of age and older) study, a randomized, observer-blinded study, evaluated the immunogenicity of BOOSTRIX (N = 887) compared with a US-licensed comparator Td vaccine (N = 445) (Sanofi Pasteur SA). Vaccines were administered as a single dose to subjects who had not received a tetanus-diphtheria booster within 5 years. Among all vaccine recipients, the mean age was approximately 72 years of age; 54% were female and 95% were white. The immune responses to each of the antigens contained in BOOSTRIX were evaluated in sera obtained approximately 1 month after administration.

##### **Response to Tetanus and Diphtheria Toxoids and Pertussis Antigens**

Immune responses to tetanus and diphtheria toxoids and pertussis antigens were measured 1 month after administration of a single dose of BOOSTRIX or a comparator Td vaccine. Anti-tetanus and anti-diphtheria seroprotective rates ( $\geq 0.1$  IU/mL) were comparable between BOOSTRIX and the comparator Td vaccine (Table 12).

**Table 12. Immune Responses to Tetanus and Diphtheria Toxoids following BOOSTRIX or Comparator Td Vaccine in the Elderly 65 Years of Age and Older (ATP Cohort for Immunogenicity)**

	<b>BOOSTRIX</b>	<b>Td</b>
	<b>(N = 844-864)</b>	<b>(N = 430-439)</b>
Anti-tetanus		
% $\geq 0.1$ IU/mL (95% CI)	96.8 (95.4, 97.8) <sup>a</sup>	97.5 (95.6, 98.7)
% $\geq 1.0$ IU/mL (95% CI)	88.8 (86.5, 90.8) <sup>a</sup>	90.0 (86.8, 92.6)
Anti-diphtheria		
% $\geq 0.1$ IU/mL (95% CI)	84.9 (82.3, 87.2) <sup>a</sup>	86.6 (83.0, 89.6)
% $\geq 1.0$ IU/mL (95% CI)	52.0 (48.6, 55.4) <sup>b</sup>	51.2 (46.3, 56.0)

Td = Tetanus and Diphtheria Toxoids Adsorbed, a US-licensed Td vaccine, manufactured by Sanofi Pasteur SA.

ATP = According-to-protocol; CI = Confidence Interval.

<sup>a</sup> Seroprotection rates for BOOSTRIX were non-inferior to the comparator Td vaccine (lower limit of 95% CI on the difference of BOOSTRIX minus Td  $\geq -10\%$ ).

<sup>b</sup> Non-inferiority criteria not prospectively defined for this endpoint.

The GMCs to each of the pertussis antigens 1 month following a single dose of BOOSTRIX were compared with the GMCs of infants following a 3-dose primary series of INFANRIX administered at 3, 4, and 5 months of age. Table 13 presents the results for the total immunogenicity cohort in both studies (vaccinated subjects with serology data available for at least one pertussis antigen). These infants were a subset of those who formed the cohort for the German household contact study in which the efficacy of INFANRIX was demonstrated [*see Clinical Studies (14.1)*]. Although a serologic correlate of protection for pertussis has not been established, anti-PT, anti-FHA, and anti-pertactin antibody concentrations in the elderly (65 years of age and older) 1 month after a single dose of BOOSTRIX were non-inferior to those of infants following a primary vaccination series with INFANRIX.

**Table 13. Ratio of GMCs to Pertussis Antigens following One Dose of BOOSTRIX in the Elderly 65 Years of Age and Older Compared with 3 Doses of INFANRIX in Infants (Total Immunogenicity Cohort)**

	<b>GMC Ratio: BOOSTRIX/INFANRIX (95% CI)</b>
Anti-PT	1.07 (1.00, 1.15) <sup>a</sup>
Anti-FHA	8.24 (7.45, 9.12) <sup>a</sup>
Anti-pertactin	0.93 (0.79, 1.10) <sup>a</sup>

GMC = Geometric mean antibody concentration; CI = Confidence Interval.

Number of subjects for BOOSTRIX GMC evaluation: Anti-PT = 865, anti-FHA = 847, and anti-pertactin = 878.

Number of subjects for INFANRIX GMC evaluation: Anti-PT = 2,884, anti-FHA = 685, and anti-pertactin = 631.

<sup>a</sup> BOOSTRIX was non-inferior to INFANRIX (lower limit of 95% CI for the GMC ratio of BOOSTRIX/INFANRIX  $\geq 0.67$ ).

## **14.5 Concomitant Vaccine Administration**

### **Concomitant Administration with Meningococcal Conjugate Vaccine**

The concomitant use of BOOSTRIX and a tetravalent meningococcal (groups A, C, Y, and W-135) conjugate vaccine (Sanofi Pasteur SA) was evaluated in a randomized study in healthy adolescents 11 to 18 years of age. A total of 1,341 adolescents were vaccinated with BOOSTRIX. Of these, 446 subjects received BOOSTRIX administered concomitantly with meningococcal conjugate vaccine at different injection sites, 446 subjects received BOOSTRIX followed by meningococcal conjugate vaccine 1 month later, and 449 subjects received meningococcal conjugate vaccine followed by BOOSTRIX 1 month later.

Immune responses to diphtheria and tetanus toxoids (% of subjects with anti-tetanus and anti-diphtheria antibodies  $\geq 1.0$  IU/mL by ELISA), pertussis antigens (booster responses and GMCs), and meningococcal antigens (vaccine responses) were measured 1 month (range: 30 to 48 days) after concomitant or separate administration of BOOSTRIX and meningococcal conjugate vaccine. For BOOSTRIX given concomitantly with meningococcal conjugate vaccine compared with BOOSTRIX administered first, non-inferiority was demonstrated for all antigens, with the exception of the anti-pertactin GMC. The lower limit of the 95% CI for the GMC ratio was 0.54 for anti-pertactin (pre-specified limit  $\geq 0.67$ ). For the anti-pertactin booster response, non-inferiority was demonstrated. It is not known if the efficacy of BOOSTRIX is affected by the reduced response to pertactin.

There was no evidence that BOOSTRIX interfered with the antibody responses to the meningococcal antigens when measured by serum bactericidal assays (rSBA) when given concomitantly or sequentially (meningococcal conjugate vaccine followed by BOOSTRIX or BOOSTRIX followed by meningococcal conjugate vaccine).

### Concomitant Administration with FLUARIX (Influenza Virus Vaccine)

The concomitant use of BOOSTRIX and FLUARIX was evaluated in a multicenter, open-label, randomized, controlled study of 1,497 adults 19 to 64 years of age. In one group, subjects received BOOSTRIX and FLUARIX concurrently (n = 748). The other group received FLUARIX at the first visit, then 1 month later received BOOSTRIX (n = 749). Sera was obtained prior to and 1 month following concomitant or separate administration of BOOSTRIX and/or FLUARIX, as well as 1 month after the separate administration of FLUARIX.

Immune responses following concurrent administration of BOOSTRIX and FLUARIX were non-inferior to separate administration for diphtheria (seroprotection defined as  $\geq 0.1$  IU/mL), tetanus (seroprotection defined as  $\geq 0.1$  IU/mL and based on concentrations  $\geq 1.0$  IU/mL), pertussis toxin (PT) antigen (anti-PT GMC) and influenza antigens (percent of subjects with hemagglutination-inhibition [HI] antibody titer  $\geq 1:40$  and  $\geq 4$ -fold rise in HI titer). Non-inferiority criteria were not met for the anti-pertussis antigens FHA and pertactin. The lower limit of the 95% CI of the GMC ratio was 0.64 for anti-FHA and 0.60 for anti-pertactin and the pre-specified limit was  $\geq 0.67$ . It is not known if the efficacy of BOOSTRIX is affected by the reduced response to FHA and pertactin.

## **15 REFERENCES**

1. Institute of Medicine (IOM). Stratton KR, Howe CJ, Johnston RB, eds. *Adverse events associated with childhood vaccines. Evidence bearing on causality*. Washington, DC: National Academy Press; 1994.
2. Wassilak SGF, Roper MH, Kretsinger K, and Orenstein WA. Tetanus Toxoid. In: Plotkin SA, Orenstein WA, and Offit PA, eds. *Vaccines*. 5th ed. Saunders; 2008:805-839.
3. Vitek CR and Wharton M. Diphtheria Toxoid. In: Plotkin SA, Orenstein WA, and Offit PA, eds. *Vaccines*. 5th ed. Saunders; 2008:139-156.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

BOOSTRIX is available in 0.5-mL single-dose vials and disposable prefilled TIP-LOK syringes (packaged without needles):

NDC 58160-842-01 Vial in Package of 10: NDC 58160-842-11

NDC 58160-842-05 Syringe in Package of 1: NDC 58160-842-34

NDC 58160-842-43 Syringe in Package of 10: NDC 58160-842-52

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen.

**17 PATIENT COUNSELING INFORMATION**

The patient, parent, or guardian should be:

- informed of the potential benefits and risks of immunization with BOOSTRIX.
- informed about the potential for adverse reactions that have been temporally associated with administration of BOOSTRIX or other vaccines containing similar components.
- instructed to report any adverse events to their healthcare provider.
- informed that safety and efficacy have not been established in pregnant women. Register women who receive BOOSTRIX while pregnant in the pregnancy registry by calling 1-888-452-9622.
- given the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).

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BTX:XXPI

# **EXHIBIT 256**



**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use Adacel safely and effectively. See full prescribing information for Adacel.**

**Adacel (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed), Suspension for Intramuscular Injection**  
Initial U.S. Approval: 2005

**RECENT MAJOR CHANGES**

Indications and Usage (1) 01/2019  
Dosage and Administration (2.2) 01/2019

**INDICATIONS AND USAGE**

- Adacel is a vaccine indicated for active booster immunization against tetanus, diphtheria and pertussis. Adacel is approved for use in persons 10 through 64 years of age. (1)

**DOSAGE AND ADMINISTRATION****For intramuscular injection only.**

- Each dose of Adacel is administered as a 0.5 mL injection. (2.1)
- For routine booster vaccination, a first dose of Adacel is administered 5 years or more after the last dose of Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) series or 5 years or more after vaccination with Tetanus and Diphtheria Toxoids Adsorbed (Td). A second dose of Adacel may be administered 8 years or more after the first dose with Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap).
- Adacel may be administered for tetanus prophylaxis for wound management. For management of a tetanus prone wound, a booster dose of Adacel may be administered if at least 5 years have elapsed since previous receipt of a tetanus toxoid containing vaccine. (2.2)

**DOSAGE FORMS AND STRENGTHS**

- Single-dose vials and prefilled syringes containing a 0.5 mL suspension for injection. (3)

**CONTRAINDICATIONS**

- Severe allergic reaction (eg, anaphylaxis) to any component of Adacel or any other diphtheria toxoid, tetanus toxoid and pertussis antigen-containing vaccine. (4.1)
- Encephalopathy (eg, coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous pertussis antigen-containing vaccine. (4.2)

**WARNINGS AND PRECAUTIONS**

- The tip caps of the prefilled syringes may contain natural rubber latex, which may cause allergic reactions in latex sensitive individuals. (5.2, 17)
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following a subsequent dose of Adacel vaccine. (5.3)

- Progressive or unstable neurologic conditions are reasons to defer Adacel vaccination. (5.4)
- Persons who experienced an Arthus-type hypersensitivity reaction following a prior dose of a tetanus toxoid-containing vaccine should not receive Adacel unless at least 10 years have elapsed since the last dose of a tetanus toxoid-containing vaccine. (5.5)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including Adacel. Procedures should be in place to prevent falling injury and manage syncopal reactions. (5.7)

**ADVERSE REACTIONS**

- Following the first vaccination with Adacel, the most common solicited adverse reactions within 0-14 days of vaccination for Adolescents (11-17 years of age)/Adults (18-64 years of age) were: injection site pain (77.8%/65.7%), headache (43.7%/33.9%), body ache or muscle weakness (30.4%/21.9%), tiredness (30.2%/24.3%), injection site swelling (20.9%/21.0%), and injection site erythema (20.8%/24.7%). (6.1)
- Following a second vaccination with Adacel, the most common solicited reactions occurring within 0-7 days of vaccination for Adults (18-64 years of age) were: injection site pain (87.1%), myalgia (58.1%), headache (41.4%), malaise (33.3%), injection site swelling (6.9%), and injection site erythema (6.4%). (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or <http://vaers.hhs.gov>.**

**DRUG INTERACTIONS**

- When Adacel was administered concomitantly with trivalent inactivated influenza vaccine (TIV) to adults 19-64 years of age, a lower antibody response was observed for pertactin antigen as compared to Adacel administered alone. (7.1, 14.4)
- Immunosuppressive therapies may reduce the immune response to Adacel. (7.2)
- Do not mix Adacel with any other vaccine in the same syringe or vial.

**USE IN SPECIFIC POPULATIONS**

- Pregnancy Exposure Registry: contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE). (8.1)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 01/2019**

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

Adacel® is a vaccine indicated for active booster immunization against tetanus, diphtheria and pertussis. Adacel is approved for use in individuals 10 through 64 years of age.

### **2 DOSAGE AND ADMINISTRATION**

**For intramuscular injection only.**

#### **2.1 Preparation for Administration**

Just before use, shake the vial or syringe well until a uniform, white, cloudy suspension results.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exist, the vaccine should not be administered.

Withdraw the 0.5 mL dose of vaccine from the single-dose vial using a sterile needle and syringe.

Adacel should not be combined through reconstitution or mixed with any other vaccine.

#### **2.2 Administration, Dose and Schedule**

Adacel is administered as a single 0.5 mL intramuscular injection.

##### **Routine Booster Vaccination**

A first dose of Adacel is administered 5 years or more after the last dose of the Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) series or 5 years or more after a dose of Tetanus and Diphtheria Toxoids Adsorbed (Td). A second dose of Adacel may be administered 8 years or more after the first dose of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap).

##### **Wound Management**

Adacel may be administered for tetanus prophylaxis for wound management. For management of a tetanus prone wound, a booster dose of Adacel may be administered if at least 5 years have elapsed since previous receipt of a tetanus toxoid containing vaccine.

### **3 DOSAGE FORMS AND STRENGTHS**

Adacel is a suspension for injection available in 0.5 mL single-dose vials and prefilled syringes. [See *HOW SUPPLIED/STORAGE AND HANDLING* (16).]

## **4 CONTRAINDICATIONS**

### **4.1 Hypersensitivity**

A severe allergic reaction (eg, anaphylaxis) after a previous dose of any tetanus toxoid, diphtheria toxoid or pertussis containing vaccine or any other component of this vaccine is a contraindication to administration of Adacel. [See *DESCRIPTION (11)*.] Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.

### **4.2 Encephalopathy**

Encephalopathy (eg, coma, prolonged seizures, or decreased level of consciousness) within 7 days of a previous dose of a pertussis containing vaccine not attributable to another identifiable cause is a contraindication to administration of any pertussis containing vaccine, including Adacel.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Management of Acute Allergic Reactions**

Epinephrine hydrochloride solution (1:1,000) and other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

### **5.2 Latex**

For one presentation of Adacel, the tip caps of the prefilled syringes may contain natural rubber latex, which may cause allergic reactions in latex sensitive individuals. The vial stopper is not made with natural rubber latex. [See *HOW SUPPLIED/STORAGE AND HANDLING (16)*.]

### **5.3 Guillain-Barré Syndrome and Brachial Neuritis**

A review by the Institute of Medicine found evidence for acceptance of a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. (1) If Guillain-Barré syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following a dose of Adacel.

### **5.4 Progressive or Unstable Neurologic Disorders**

Progressive or unstable neurologic conditions are reasons to defer Adacel. It is not known whether administration of Adacel to persons with an unstable or progressive neurologic disorder might hasten manifestations of the disorder or affect the prognosis. Administration of Adacel to persons with an unstable or progressive neurologic disorder may result in diagnostic confusion between manifestations of the underlying illness and possible adverse effects of vaccination.

## 5.5 Arthus-Type Hypersensitivity

Persons who experienced an Arthus-type hypersensitivity reaction following a prior dose of a tetanus toxoid-containing vaccine should not receive Adacel unless at least 10 years have elapsed since the last dose of a tetanus toxoid containing vaccine.

## 5.6 Altered Immunocompetence

If Adacel is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained. [See *DRUG INTERACTIONS* (7.2).]

## 5.7 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccine, including Adacel. Procedures should be in place to prevent falling injury and manage syncopal reactions.

# 6 ADVERSE REACTIONS

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events. As with any vaccine, there is the possibility that broad use of Adacel could reveal adverse reactions not observed in clinical trials.

The safety of a first vaccination with Adacel was evaluated in 5 clinical studies. Three of the studies were conducted in the U.S. and 2 were conducted in Canada. Of the study participants, 86% were Caucasian, 8% Black, 3% Hispanic, 1% Asian and 2% of other ethnic origin. A total of 7,143 individuals 10 through 64 years of age inclusive (4,695 adolescents 10 through 17 years of age and 2,448 adults 18 through 64 years of age) received a single dose of Adacel.

### U.S. Adolescent and Adult Study of a First Vaccination with Adacel (Td506)

Clinical study Td506 was a randomized, observer-blind, active-controlled trial that enrolled adolescents 11 through 17 years of age (Adacel N = 1,184; DECAVAC (Tetanus and Diphtheria Toxoids Adsorbed; manufactured by Sanofi Pasteur Inc., Swiftwater, PA) N = 792) and adults 18 through 64 years of age (Adacel N = 1,752; DECAVAC N = 573). Study participants had not received tetanus or diphtheria-containing vaccines within the previous 5 years. Solicited local and systemic reactions and unsolicited adverse events were monitored daily for 14 days post vaccination using a diary card. From days 14 to 28 post vaccination, information on adverse events necessitating a medical contact, such as a telephone call, visit to an emergency room, physician's office or hospitalization, was obtained via telephone interview or at an interim clinic visit. From days 28 to 6 months post vaccination, participants were monitored for unexpected

visits to a physician's office or to an emergency room, onset of serious illness, and hospitalizations. Information regarding adverse events that occurred in the 6-month post vaccination time period was obtained from participants via telephone contact. At least 96% of participants completed the 6-month follow-up evaluation.

The frequency of selected solicited adverse reactions (erythema, swelling, pain and fever) occurring during days 0 to 14 following vaccination with Adacel or Td vaccine in adolescents 11 through 17 years of age and adults 18 through 64 years of age are presented in Table 1. Most of these reactions were reported at a similar frequency in recipients of both Adacel and Td vaccine. Pain at the injection site was the most common adverse reaction in 62.9% to 77.8% of all vaccinees. In addition, overall rates of pain were higher in adolescent recipients of Adacel compared to Td vaccine recipients. Rates of moderate and severe pain in adolescents did not significantly differ between the Adacel and Td vaccine groups. Among adults, the rates of pain after receipt of Adacel or Td vaccine did not significantly differ. Fever of 38°C and higher was uncommon, although in the adolescent age group it occurred significantly more frequently in Adacel recipients than Td vaccine recipients.

**Table 1: Frequencies of Solicited Injection Site Reactions and Fever for Adolescents and Adults, Days 0-14, Following a First Vaccination with Adacel or Td Vaccine in Study Td506**

Adverse Reactions*		Adolescents 11-17 years		Adults 18-64 years	
		Adacel N <sup>†</sup> = 1,170-1,175 (%)	Td <sup>‡</sup> N <sup>†</sup> = 783-787 (%)	Adacel N <sup>†</sup> = 1,688-1,698 (%)	Td <sup>‡</sup> N <sup>†</sup> = 551-561 (%)
Injection Site Pain	Any	77.8 <sup>§</sup>	71.0	65.7	62.9
	Moderate**	18.0	15.6	15.1	10.2
	Severe <sup>††</sup>	1.5	0.6	1.1	0.9
Injection Site Swelling	Any	20.9	18.3	21.0	17.3
	Moderate**				
	1.0 to 3.4 cm	6.5	5.7	7.6	5.4
	Severe <sup>††</sup>				
	≥3.5 cm	6.4	5.5	5.8	5.5
	≥5 cm (2 inches)	2.8	3.6	3.2	2.7
Injection Site Erythema	Any	20.8	19.7	24.7	21.6
	Moderate**				
	1.0 to 3.4 cm	5.9	4.6	8.0	8.4
	Severe <sup>††</sup>				
	≥3.5 cm	6.0	5.3	6.2	4.8
	≥5 cm (2 inches)	2.7	2.9	4.0	3.0
Fever	≥38.0°C (≥100.4°F)	5.0 <sup>§</sup>	2.7	1.4	1.1
	≥38.8°C to ≤39.4°C (≥102.0°F to ≤103.0°F)	0.9	0.6	0.4	0.2
	≥39.5°C (≥103.1°F)	0.2	0.1	0.0	0.2

\* The study sample size was designed to detect >10% differences between Adacel and Td vaccines for events of

‘Any’ intensity.

† N = number of participants with available data.

‡ Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur Inc., Swiftwater, PA.

§ Adacel did not meet the non-inferiority criterion for rates of ‘Any’ Pain in adolescents compared to Td vaccine rates (upper limit of the 95% CI on the difference for Adacel minus Td vaccine was 10.7% whereas the criterion was <10%). For ‘Any’ Fever the non-inferiority criteria was met, however, ‘Any’ Fever was statistically higher in adolescents receiving Adacel.

\*\* Interfered with activities, but did not necessitate medical care or absenteeism.

†† Incapacitating, prevented the performance of usual activities, may have/or did necessitate medical care or absenteeism.

The frequency of other solicited adverse reactions (days 0-14) are presented in Table 2. The rates of these reactions following a first vaccination with Adacel were comparable with those observed with Td vaccine. Headache was the most frequent systemic reaction and was usually of mild to moderate intensity.

**Table 2: Frequencies of Other Solicited Adverse Reactions for Adolescents and Adults, Days 0-14, Following a First Vaccination with Adacel or Td Vaccine in Study Td506**

Adverse Reaction		Adolescents 11-17 years		Adults 18-64 years	
		Adacel N* = 1,174-1,175 (%)	Td† N* = 787 (%)	Adacel N* = 1,697-1,698 (%)	Td† N* = 560-561 (%)
Headache	Any	43.7	40.4	33.9	34.1
	Moderate‡	14.2	11.1	11.4	10.5
	Severe§	2.0	1.5	2.8	2.1
Body Ache or Muscle Weakness	Any	30.4	29.9	21.9	18.8
	Moderate‡	8.5	6.9	6.1	5.7
	Severe§	1.3	0.9	1.2	0.9
Tiredness	Any	30.2	27.3	24.3	20.7
	Moderate‡	9.8	7.5	6.9	6.1
	Severe§	1.2	1.0	1.3	0.5
Chills	Any	15.1	12.6	8.1	6.6
	Moderate‡	3.2	2.5	1.3	1.6
	Severe§	0.5	0.1	0.7	0.5
Sore and Swollen Joints	Any	11.3	11.7	9.1	7.0
	Moderate‡	2.6	2.5	2.5	2.1
	Severe§	0.3	0.1	0.5	0.5
Nausea	Any	13.3	12.3	9.2	7.9
	Moderate‡	3.2	3.2	2.5	1.8
	Severe§	1.0	0.6	0.8	0.5
Lymph Node Swelling	Any	6.6	5.3	6.5	4.1
	Moderate‡	1.0	0.5	1.2	0.5
	Severe§	0.1	0.0	0.1	0.0
Diarrhea	Any	10.3	10.2	10.3	11.3
	Moderate‡	1.9	2.0	2.2	2.7
	Severe§	0.3	0.0	0.5	0.5
Vomiting	Any	4.6	2.8	3.0	1.8
	Moderate‡	1.2	1.1	1.0	0.9
	Severe§	0.5	0.3	0.5	0.2
Rash	Any	2.7	2.0	2.0	2.3

\* N = number of participants with available data.

† Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur Inc., Swiftwater, PA.

\* Interfered with activities, but did not necessitate medical care or absenteeism.

§ Incapacitating, prevented the performance of usual activities, may have/or did necessitate medical care or absenteeism.

Injection site and systemic solicited reactions occurred at similar rates in Adacel and Td vaccine recipients in the 3 day post-vaccination period. Most injection site reactions occurred within the first 3 days after vaccination (with a mean duration of less than 3 days). The rates of unsolicited adverse events reported from days 14-28 post-vaccination were comparable between the two vaccine groups, as were the rates of unsolicited adverse events from day 28 through 6 months. There were no spontaneous reports of extensive limb swelling of the injected limb in study Td506, nor in the other three studies which also contributed to the safety database for Adacel.

#### Adult Study of a Second Vaccination with Adacel (Td537)

In a randomized, observer-blind, active-controlled, multi-center study (Td537), adults 18 through 64 years of age who had received a first dose of Adacel 8-12 years previously were enrolled and randomized to receive either Adacel (N = 1002) or a US licensed Td vaccine, TENIVAC (Tetanus and Diphtheria Toxoids Adsorbed; manufactured by Sanofi Pasteur, Limited) (N = 328). Subjects were recruited from the primary licensure study Td506 and the Canadian general public and had not received Td or Tdap vaccine since their initial Adacel dose. The demographic characteristics for study participants were similar for both vaccine groups. The mean ages were 28.9 years for the Adacel group and 29.2 years for the Td group. Overall, there were more female participants in both the Adacel group and Td group; 64.5% and 64.6%, respectively. In both vaccine groups, greater than 94% of subjects identified as white and 99% as non-Hispanic or Latino.

Safety data were collected from all participants who received the study vaccine (N = 999 for the Adacel group; N = 328 for the Td group). Solicited local and systemic reactions and unsolicited adverse events were monitored for 7 days post-vaccination using a diary card. Unsolicited adverse events were collected for approximately 28 days post-vaccination. Serious adverse events were collected throughout the study period (up to 6 months post-vaccination).

Solicited adverse reactions reported to occur during days 0-7 following vaccination are presented in Table 3.



**Table 3: Frequencies of Solicited Adverse Reactions 0-7 Days Following a Second Vaccination with Adacel Compared to Td Vaccine in Study Td537 - Safety Analysis Set**

Adverse Reaction		Adacel (N=999) (%)	Td Adsorbed <sup>§</sup> (N=328) (%)
Injection site pain	Any	87.1	87.4
	Grade 2*	28.5	31.4
	Grade 3 <sup>†</sup>	3.6	2.8
Injection site erythema	Any	6.4	5.5
	Grade 2 (≥51 to ≤100 mm)	2.1	2.8
	Grade 3 (>100 mm)	0.2	0.0
Injection site swelling	Any	6.9	8.0
	Grade 2 (≥51 to ≤100 mm)	2.4	2.2
	Grade 3 (>100 mm)	0.3	0.0
Fever	Any	0.9	1.8
	Grade 2 (≥38.5°C to ≤38.9°C or ≥101.2°F to ≤102.0°F)	0.3	0.6
	Grade 3 (≥102.1°F)	0.2	0.3
Headache	Any	41.4	39.1
	Grade 2*	12.4	10.5
	Grade 3 <sup>†</sup>	2.6	4.0
Malaise	Any	33.3	30.8
	Grade 2*	9.3	9.8
	Grade 3 <sup>†</sup>	3.0	3.7
Myalgia	Any	58.1	58.2
	Grade 2*	18.7	16.9
	Grade 3 <sup>†</sup>	3.0	3.1

N = number of participants with available data

\* Some interference with activity

† Significant; prevents daily activity

§ Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur Limited, Toronto, Ontario, Canada.

**Adult Study of a Second Vaccination with Adacel (Td518)**

Study Td518 was a descriptive, open-label, post-marketing, multi-center study evaluating the safety of Adacel readministration in adults 5 years following a previous dose of Adacel. The mean age of subjects was 31.7 years, there were more females (52.2%) than males (47.8%) and 89.9% of subjects were Caucasian. Solicited adverse reactions were collected for 14 days following vaccination. SAEs were monitored for 6 months following vaccination. A total of 545 subjects 16-69 years of age were enrolled. All participants in this study received a first dose of Adacel vaccine as part of Sanofi Pasteur studies Td501, Td502, or Td505. Approximately 90% of the participants had at least one solicited injection site reaction. The most frequently reported injection site reactions were pain in 87.6% of subjects, followed by erythema/redness in 28.6%, and swelling in 25.6%. Approximately 77% of the participants had at least one solicited systemic

reaction. The most frequently reported solicited systemic adverse reactions in subjects who received a second dose of Adacel were myalgia (61%), followed by headache (53.2%), malaise (38.2%), and fever (6.5%).

#### Injection Site and Systemic Reactions Following Adacel Given Concomitantly with Hepatitis B Vaccine

In the concomitant vaccination study with Adacel (first vaccination) and Hepatitis B vaccine [Recombivax HB] (Td501) [See *CLINICAL STUDIES (14)*], injection site and systemic adverse events were monitored daily for 14 days post-vaccination using a diary card. Injection site adverse events were only monitored at site/arm of Adacel administration. Unsolicited reactions (including immediate reactions, serious adverse events and events that elicited seeking medical attention) were collected at a clinic visit or via telephone interview for the duration of the trial, ie, up to 6 months post-vaccination.

The rates reported for fever and injection site pain (at the Adacel administration site) were similar when Adacel and Hepatitis B vaccine were given concurrently or separately. However, the rates of injection site erythema (23.4% for concomitant vaccination and 21.4% for separate administration) and swelling (23.9% for concomitant vaccination and 17.9% for separate administration) at the Adacel administration site were increased when coadministered. Swollen and/or sore joints were reported by 22.5% for concomitant vaccination and 17.9% for separate administration. The rates of generalized body aches in the individuals who reported swollen and/or sore joints were 86.7% for concomitant vaccination and 72.2% for separate administration. Most joint complaints were mild in intensity with a mean duration of 1.8 days. The incidence of other solicited and unsolicited adverse events were not different between the 2 study groups.

#### Injection Site and Systemic Reactions Following Adacel Given Concomitantly with Trivalent Inactivated Influenza Vaccine (TIV)

In the concomitant vaccination study with Adacel (first vaccination) and trivalent inactivated influenza vaccine [Fluzone] (Td502) [See *CLINICAL STUDIES (14)*], injection site and systemic adverse events were monitored for 14 days post-vaccination using a diary card. All unsolicited reactions occurring through day 14 were collected. From day 14 to the end of the trial, ie, up to 84 days, only events that elicited seeking medical attention were collected.

The rates of fever and injection site erythema and swelling were similar for recipients of concurrent and separate administration of Adacel and TIV. However, pain at the Adacel injection site occurred at statistically higher rates following concurrent administration (66.6%) versus separate administration (60.8%). The rates of sore and/or swollen joints were 13% for concurrent administration and 9% for separate administration. Most joint complaints were mild in intensity with a mean duration of 2.0 days. The incidence of other solicited and unsolicited adverse events was similar between the 2 study groups.

#### Additional Studies

In an additional study (Td505), 1,806 adolescents 11 through 17 years of age received Adacel (first vaccination) as part of the lot consistency study used to support Adacel licensure. This

study was a randomized, double-blind, multi-center trial designed to assess lot consistency as measured by the safety and immunogenicity of 3 lots of Adacel when given as a booster dose to adolescents 11 through 17 years of age inclusive. Local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. Unsolicited adverse events and serious adverse events were collected for 28 days post-vaccination. Pain was the most frequently reported local adverse event occurring in approximately 80% of all participants. Headache was the most frequently reported systemic event occurring in approximately 44% of all participants. Sore and/or swollen joints were reported by approximately 14% of participants. Most joint complaints were mild in intensity with a mean duration of 2.0 days.

An additional 962 adolescents and adults received Adacel in three supportive Canadian studies (TC9704, Td9707 and TD9805) used as the basis for licensure in other countries. Within these clinical trials, the rates of local and systemic reactions following the first vaccination with Adacel were similar to those reported in the four principal trials in the U.S. with the exception of a higher rate (86%) of adults experiencing “any” local injection site pain. The rate of severe pain (0.8%), however, was comparable to the rates reported in four principal trials conducted in the US. There was one spontaneous report of whole-arm swelling of the injected limb among the 277 Td vaccine recipients, and two spontaneous reports among the 962 Adacel recipients in the supportive Canadian studies.

An additional study (Td519) enrolled 1,302 individuals in an open label, two-arm, multicenter trial (651 participants in each group) to evaluate the safety and immunogenicity of a first vaccination with Adacel administered to persons 10 to <11 years of age compared to persons 11 to <12 years of age. Immediate reactions were monitored for 20 minutes post-vaccination. Solicited local and systemic adverse events were monitored for 7 days post-vaccination using a diary card. Unsolicited and serious adverse events were collected for approximately 30 days post-vaccination. Similar rates of immediate, solicited and unsolicited adverse reactions were reported in each of the two age cohorts. One serious adverse event, not related to vaccination, was reported in the younger age group.

### Serious Adverse Events

Throughout the 6-month follow-up period following a first vaccination with Adacel in study Td506, SAEs were reported in 1.5% of Adacel recipients and in 1.4% of Td vaccine recipients. Two SAEs in adults were neuropathic events that occurred within 28 days of Adacel administration; one severe migraine with unilateral facial paralysis and one diagnosis of nerve compression in neck and left arm. Similar or lower rates of serious adverse events were reported in the other trials following a first vaccination with Adacel in participants up to 64 years of age and no additional neuropathic events were reported.

In study Td537 when a second vaccination of Adacel was administered 8-12 years following the initial vaccination of Adacel, a total of 8 participants (0.8%) in the Adacel group and 1 participant (0.3%) in the Td group reported SAEs during the 6-month follow-up period. All SAEs were considered by the investigator to be unrelated to the study vaccine.

In study Td518, seven participants experienced an SAE, all of which were considered by the investigator to be unrelated to the study vaccine.

## 6.2 Postmarketing Experience

The following adverse events of Adacel have been spontaneously reported in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it may not be possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

The following adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to Adacel.

- ***Immune system disorders***  
Anaphylactic reaction, hypersensitivity reaction (angioedema, edema, rash, hypotension)
- ***Nervous system disorders***  
Paresthesia, hypoesthesia, Guillain-Barré syndrome, brachial neuritis, facial palsy, convulsion, syncope, myelitis
- ***Cardiac disorders***  
Myocarditis
- ***Skin and subcutaneous tissue disorders***  
Pruritus, urticaria
- ***Musculoskeletal and connective tissue disorders***  
Myositis, muscle spasm
- ***General disorders and administration site conditions***  
Large injection site reactions (>50 mm), extensive limb swelling from the injection site beyond one or both joints  
Injection site bruising, sterile abscess, Arthus hypersensitivity

## 7 DRUG INTERACTIONS

### 7.1 Concomitant Vaccine Administration

When Adacel is administered concomitantly with other injectable vaccines or Tetanus Immune Globulin, they should be given with separate syringes and at different injection sites. Adacel should not be mixed with any other vaccine in the same syringe or vial.

#### Trivalent Inactivated Influenza Vaccine (TIV)

In a clinical study Adacel (first vaccination) was administered concomitantly with a US-licensed trivalent inactivated influenza vaccine (TIV). [See *ADVERSE REACTIONS (6.1)* and *CLINICAL STUDIES (14)*.]

No interference in tetanus and diphtheria seroprotection rates and responses to influenza vaccine, detoxified pertussis toxin (PT), fimbriae types 2 and 3 (FIM) or filamentous hemagglutinin (FHA) were observed when Adacel vaccine was administered concomitantly with TIV compared to separate administration. A lower pertactin (PRN) GMC was observed when Adacel was administered concomitantly with TIV compared to separate administration.

## 7.2 Immunosuppressive Treatments

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. [See *WARNINGS AND PRECAUTIONS* (5.6).]

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Adacel during pregnancy. Women who receive Adacel during pregnancy are encouraged to contact directly, or have their healthcare professional contact, Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE).

#### Risk Summary

All pregnancies have a risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are no adequate and well-controlled studies of Adacel administration in pregnant women in the U.S.

Available data suggest the rates of major birth defects and miscarriage in women who receive Adacel within 30 days prior to pregnancy or during pregnancy are consistent with estimated background rates. (See *Data*)

Two developmental toxicity studies were performed in female rabbits given 0.5 mL (a single human dose) of Adacel twice prior and during gestation. The studies revealed no evidence of harm to the fetus due to Adacel. (See *Data*)

#### Data

##### *Human Data*

An assessment of data from the ongoing pregnancy registry over 12 years (2005-2017) included 1518 reports of exposure to Adacel vaccine from 30 days before or at any time during pregnancy. Of these reports, 543 had known pregnancy outcomes available and were enrolled in the registry prior to the outcomes being known. Among the 543 pregnancies with known outcomes, the timing of Adacel vaccination was not known for 126 of the pregnancies.

Of the prospectively followed pregnancies for whom the timing of Adacel vaccination was known, 374 women received Adacel during the 30 days prior to conception through the second trimester. Outcomes among these prospectively followed pregnancies included 5 infants with major birth defects and 25 cases of miscarriage.

### ***Animal Data***

The effect of Adacel on embryo-fetal and pre-weaning development was evaluated in two developmental toxicity studies in female rabbits. Animals were administered 0.5 mL (a single human dose) of Adacel twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study.

## **8.2 Lactation**

### ***Risk Summary***

It is not known whether Adacel vaccine components are excreted in human milk. Data are not available to assess the effect of administration of Adacel on breast-fed infants or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Adacel and any potential adverse effects on the breastfed child from Adacel or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine

## **8.4 Pediatric Use**

Adacel is not approved for individuals less than 10 years of age. Safety and effectiveness of Adacel in persons less than 10 years of age in the U.S. have not been established.

## **8.5 Geriatric Use**

Adacel is not approved for use in individuals 65 years of age and older.

In a clinical study, individuals 65 years of age and older received a single dose of Adacel. Based on prespecified criteria, persons 65 years of age and older who received a dose of Adacel had lower geometric mean concentrations of antibodies to PT, PRN and FIM when compared to infants who had received a primary series of DAPTACEL<sup>®</sup>, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP). [See *CLINICAL STUDIES (14)* for description of DAPTACEL.]

## **11 DESCRIPTION**

Adacel is a sterile isotonic suspension of tetanus and diphtheria toxoids and pertussis antigens adsorbed on aluminum phosphate, for intramuscular injection.

Each 0.5 mL dose contains 5 Lf tetanus toxoid (T), 2 Lf diphtheria toxoid (d), and acellular pertussis antigens [2.5 mcg detoxified pertussis toxin (PT), 5 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)]. Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, ≤5 mcg residual formaldehyde, <50 ng residual glutaraldehyde and 3.3 mg (0.6% v/v) 2-phenoxyethanol

(not as a preservative). The antigens are the same as those in DAPTACEL; however, Adacel is formulated with reduced quantities of diphtheria and detoxified PT.

The acellular pertussis vaccine components are produced from *Bordetella pertussis* cultures grown in Stainer-Scholte medium (2) modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium. FIM are extracted and copurified from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde, FHA is treated with formaldehyde, and the residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed onto aluminum phosphate.

The tetanus toxin is produced from *Clostridium tetani* grown in modified Mueller-Miller casamino acid medium without beef heart infusion. (3) Tetanus toxin is detoxified with formaldehyde and purified by ammonium sulfate fractionation and diafiltration. *Corynebacterium diphtheriae* is grown in modified Mueller's growth medium. (4) After purification by ammonium sulfate fractionation, diphtheria toxin is detoxified with formaldehyde and diafiltered.

The adsorbed diphtheria, tetanus and acellular pertussis components are combined with aluminum phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for injection. Adacel does not contain a preservative.

In the guinea pig potency test, the tetanus component induces at least 2 neutralizing units/mL of serum and the diphtheria component induces at least 0.5 neutralizing units/mL of serum. The potency of the acellular pertussis vaccine components is evaluated by the antibody response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by enzyme-linked immunosorbent assay (ELISA).

Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

#### Tetanus

Tetanus is a disease manifested primarily by neuromuscular dysfunction caused by a potent exotoxin released by *C tetani*.

Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay is considered the minimum protective level. (5) (6)

#### Diphtheria

Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of



protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (5) Levels of 1.0 IU/mL have been associated with long-term protection. (7)

### Pertussis

Pertussis (whooping cough) is a respiratory disease caused by *B pertussis*. This Gram-negative coccobacillus produces a variety of biologically active components, though their role in either the pathogenesis of, or immunity to, pertussis has not been clearly defined.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Adacel has not been evaluated for carcinogenic or mutagenic potential, or impairment of male fertility.

## **14 CLINICAL STUDIES**

The effectiveness of the tetanus toxoid and diphtheria toxoid used in Adacel was based on the immune response to these antigens compared to a US licensed Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) vaccine manufactured by Sanofi Pasteur Inc., Swiftwater, PA. The primary measures for immune response to the diphtheria and tetanus toxoids were the percentage of participants attaining an antibody level of at least 0.1 IU/mL.

The effectiveness of the pertussis antigens used in Adacel was evaluated based on a comparison of pertussis antibody levels achieved in recipients of Adacel with those obtained in infants after three or four doses of DAPTACEL. For the first dose of Adacel, the comparisons were to infants who received three doses of DAPTACEL in the Sweden I Efficacy trial. For the second dose of Adacel, for the evaluation of FHA, PRN, and FIM antibody levels, the comparisons were to infants who received three doses of DAPTACEL in the Sweden I Efficacy trial; for evaluation of PT antibody levels, the comparison was to infants who received four doses of DAPTACEL in a US safety and immunogenicity study (Study M5A10). In the Sweden I Efficacy Trial, three doses of DAPTACEL vaccine were shown to confer a protective efficacy of 84.9% (95% CI: 80.1%, 88.6%) against WHO defined pertussis (21 days of paroxysmal cough with laboratory-confirmed *B pertussis* infection or epidemiological link to a confirmed case). The protective efficacy against mild pertussis (defined as at least one day of cough with laboratory-confirmed *B. pertussis* infection) was 77.9% (95% CI: 72.6%, 82.2%). (8)

In addition, the ability of Adacel to elicit a booster response (defined as rise in antibody concentration after vaccination) to the tetanus, diphtheria and pertussis antigens following vaccination was evaluated.

### **14.1 Immunological Evaluation in Adolescents and Adults, 11 through 64 Years of Age Following a First Vaccination with Adacel**

Study Td506 was a comparative, multi-center, randomized, observer-blind, controlled trial which enrolled 4,480 participants; 2,053 adolescents (11-17 years of age) and 2,427 adults (18-64 years

of age). Enrollment was stratified by age to ensure adequate representation across the entire age range. Participants had not received a tetanus or diphtheria toxoid containing vaccine within the previous 5 years. After enrollment participants were randomized to receive one dose of either Adacel or Td vaccine. A total of 4,461 randomized participants were vaccinated. The per-protocol immunogenicity subset included 1,270 Adacel recipients and 1,026 Td vaccine recipients. Sera were obtained before and approximately 35 days after vaccination. [Blinding procedures for safety assessments are described in *ADVERSE REACTIONS* (6).]

Demographic characteristics were similar within age groups and between the vaccine groups. A total of 76% of the adolescents and 1.1% of the adults reported a history of receiving 5 previous doses of diphtheria-tetanus-pertussis containing vaccines. Anti-tetanus and anti-diphtheria seroprotection rates ( $\geq 0.1$  IU/mL) and booster response rates were comparable between Adacel and Td vaccines. (See Table 4 and Table 5.) Adacel induced pertussis antibody levels that were non-inferior to those of Swedish infants who received three doses of DAPTACEL vaccine (Sweden I Efficacy Study). (See Table 6.) Acceptable booster responses to each of the pertussis antigens were also demonstrated, ie, the percentage of participants with a booster response exceeded the predefined lower limit. (See Table 7.)

**Table 4: Pre-vaccination and Post-vaccination Antibody Responses and Booster Response Rates to Tetanus Toxoid Following A First Vaccination with Adacel Vaccine as Compared to Td Vaccine in Adolescents and Adults 11 through 64 Years of Age (Td506)**

Age Group (years)	Vaccine	N*	Anti-Tetanus toxoid (IU/mL)				
			Pre-vaccination		1 Month Post-vaccination		
			% $\geq 0.10$ (95% CI)	% $\geq 1.0$ (95% CI)	% $\geq 0.10$ (95% CI)	% $\geq 1.0$ (95% CI)	% Booster <sup>†</sup> (95% CI)
11-17	Adacel	527	99.6 (98.6, 100.0)	44.6 (40.3, 49.0)	100.0 <sup>‡</sup> (99.3, 100.0)	99.6 <sup>§</sup> (98.6, 100.0)	91.7 <sup>‡</sup> (89.0, 93.9)
	Td**	516	99.2 (98.0, 99.8)	43.8 (39.5, 48.2)	100.0 (99.3, 100.0)	99.4 (98.3, 99.9)	91.3 (88.5, 93.6)
18-64	Adacel	742-743	97.3 (95.9, 98.3)	72.9 (69.6, 76.1)	100.0 <sup>‡</sup> (99.5, 100.0)	97.8 <sup>§</sup> (96.5, 98.8)	63.1 <sup>‡</sup> (59.5, 66.6)
	Td**	509	95.9 (93.8, 97.4)	70.3 (66.2, 74.3)	99.8 (98.9, 100.0)	98.2 (96.7, 99.2)	66.8 (62.5, 70.9)

\* N = number of participants in the per-protocol population with available data.

<sup>†</sup> Booster response is defined as: A 4-fold rise in antibody concentration, if the pre-vaccination concentration was equal to or below the cut-off value and a 2-fold rise in antibody concentration if the pre-vaccination concentration was above the cut-off value. The cut-off value for tetanus was 2.7 IU/mL.

<sup>‡</sup> Seroprotection rates at  $\geq 0.10$  IU/mL and booster response rates to Adacel were non-inferior to Td vaccine (upper limit of the 95% CI on the difference for Td vaccine minus Adacel  $< 10\%$ ).

<sup>§</sup> Seroprotection rates at  $\geq 1.0$  IU/mL were not prospectively defined as a primary endpoint.

\*\* Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur Inc., Swiftwater, PA.

**Table 5: Pre-vaccination and Post-vaccination Antibody Responses and Booster Response Rates to Diphtheria Toxoid Following A First Vaccination with Adacel as Compared to Td Vaccine in Adolescents and Adults 11 through 64 Years of Age (Td506)**

			Anti-Diphtheria toxin (IU/mL)				
Age Group (years)	Vaccine	N*	Pre-vaccination		1 Month Post-vaccination		
			% ≥0.10 (95% CI)	% ≥1.0 (95% CI)	% ≥0.10 (95% CI)	% ≥1.0 (95% CI)	% Booster† (95% CI)
11-17	Adacel	527	72.5 (68.5, 76.3)	15.7 (12.7, 19.1)	99.8‡ (98.9, 100.0)	98.7§ (97.3, 99.5)	95.1‡ (92.9, 96.8)
	Td**	515-516	70.7 (66.5, 74.6)	17.3 (14.1, 20.8)	99.8 (98.9, 100.0)	98.4 (97.0, 99.3)	95.0 (92.7, 96.7)
18-64	Adacel	739-741	62.6 (59.0, 66.1)	14.3 (11.9, 17.0)	94.1‡ (92.1, 95.7)	78.0§ (74.8, 80.9)	87.4‡ (84.8, 89.7)
	Td**	506-507	63.3 (59.0, 67.5)	16.0 (12.9, 19.5)	95.1 (92.8, 96.8)	79.9 (76.1, 83.3)	83.4 (79.9, 86.5)

\* N = number of participants in the per-protocol population with available data.

† Booster response is defined as: A 4-fold rise in antibody concentration, if the pre-vaccination concentration was equal to or below the cut-off value and a 2-fold rise in antibody concentration if the pre-vaccination concentration was above the cut-off value. The cut-off value for diphtheria was 2.56 IU/mL.

‡ Seroprotection rates at ≥0.10 IU/mL and booster response rates to Adacel were non-inferior to Td vaccine (upper limit of the 95% CI on the difference for Td vaccine minus Adacel <10%).

§ Seroprotection rates at ≥1.0 IU/mL were not prospectively defined as a primary endpoint.

\*\* Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur Inc., Swiftwater, PA.

**Table 6: Ratio of Pertussis Antibody Geometric Mean Concentrations (GMCs)\* Observed One Month Following A First Vaccination with Adacel in Adolescents and Adults 11 through 64 Years of Age Compared with Those Observed in Infants One Month following Vaccination at 2,4 and 6 Months of Age in the Efficacy Trial with DAPTACEL (Sweden I Efficacy Study)**

	Adolescents 11-17 Years of Age	Adults 18-64 Years of Age
	Adacel†/DAPTACEL‡ GMC Ratio (95% CIs)	Adacel§/DAPTACEL‡ GMC Ratio (95% CIs)
Anti-PT	3.6 (2.8, 4.5)¶	2.1 (1.6, 2.7)¶
Anti-FHA	5.4 (4.5, 6.5)¶	4.8 (3.9, 5.9)¶
Anti-PRN	3.2 (2.5, 4.1)¶	3.2 (2.3, 4.4)¶
Anti-FIM	5.3 (3.9, 7.1)¶	2.5 (1.8, 3.5)¶

\* Antibody GMCs, measured in arbitrary ELISA units were calculated separately for infants, adolescents and adults.

† N = 524 to 526, number of adolescents in the per-protocol population with available data for Adacel.

‡ N = 80, number of infants who received DAPTACEL with available data post dose 3 (Sweden Efficacy I).

§ N = 741, number of adults in the per-protocol population with available data for Adacel.

¶ GMC following Adacel was non-inferior to GMC following DAPTACEL (lower limit of 95% CI on the ratio of GMC for Adacel divided by DAPTACEL >0.67).

**Table 7: Booster Response Rates to the Pertussis Antigens Observed One Month Following a First Vaccination with Adacel in Adolescents and Adults 11 through 64 Years of Age**

	Adolescents 11-17 Years of Age		Adults 18-64 Years of Age		Predefined Acceptable Rates* % <sup>†</sup>
	N <sup>‡</sup>	% (95% CI)	N <sup>‡</sup>	% (95% CI)	
<b>Anti-PT</b>	524	92.0 (89.3, 94.2)	739	84.4 (81.6, 87.0)	81.2
<b>Anti-FHA</b>	526	85.6 (82.3, 88.4)	739	82.7 (79.8, 85.3)	77.6
<b>Anti-PRN</b>	525	94.5 (92.2, 96.3)	739	93.8 (91.8, 95.4)	86.4
<b>Anti-FIM</b>	526	94.9 (92.6, 96.6)	739	85.9 (83.2, 88.4)	82.4

\* The acceptable response rate for each antigen was defined as the lower limit of the 95% CI for the rate being no more than 10% lower than the response rate observed in previous clinical trials.

<sup>†</sup> A booster response for each antigen was defined as a 4-fold rise in antibody concentration if the pre-vaccination concentration was equal to or below the cut-off value and a 2-fold rise in antibody concentration if the pre-vaccination concentration was above the cut-off value. The cut-off values for pertussis antigens were established based on antibody data from both adolescents and adults in previous clinical trials. The cut-off values were 85 EU/mL for PT, 170 EU/mL for FHA, 115 EU/mL for PRN and 285 EU/mL for FIM.

<sup>‡</sup> N = number of participants in the per-protocol population with available data.

Study Td519 assessed the comparative immunogenicity of a first vaccination with Adacel administered to adolescents (10 to <11 years of age and 11 to <12 years of age) [See *ADVERSE REACTIONS (6.1)*.] In this study non-inferiority was demonstrated for booster responses to tetanus and diphtheria toxoids, GMCs to the pertussis antigens (PT, FHA, PRN and FIM) and booster responses to the pertussis antigens PT, FHA and PRN. For FIM, non-inferiority was not demonstrated as the lower bound of the 95% CI of the difference in booster response rates (-5.96%) did not meet the predefined criterion (>-5% when the booster response in the older age group was >95%).

## **14.2 Immunological Evaluation in Adults, 18 through 64 Years of Age Following a Second Vaccination with Adacel**

In study Td537 [See *ADVERSE REACTIONS (6.1)*.], subjects 18 to 64 years of age who had received a dose of Adacel 8-12 years previously, were randomized to receive a second dose of Adacel or Td vaccine (Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur, Limited).. Blood samples for immunogenicity analyses were obtained from participants pre-vaccination and approximately 28 days post-vaccination. The per-protocol analysis set was used for all immunogenicity analyses, and included 948 participants in the Adacel group and 317 participants in the Td control vaccine group. Of the study participants, 35% were male. Of subjects who reported a racial/ethnic demographic, 95% were Caucasian, 2% Black, 0.5% American Indian or Alaska native, 1% Asian and 1.5% were of mixed or other origin.

A tetanus antitoxoid level of  $\geq 0.1$  IU/mL, measured by the ELISA used in this study was considered protective. An anti-diphtheria anti-toxin level of  $\geq 0.1$  IU/mL was considered protective. Pre-vaccination and post-vaccination seroprotection rates and booster response rates are presented in [Table 8](#).

**Table 8: Pre-vaccination and Post-vaccination Seroprotection Rates and Booster Response Rates to Tetanus Toxoid and Diphtheria Toxoid Following a Second Vaccination with Adacel Compared to Td Vaccine in Persons 18 through 64 Years of Age, Per Protocol Analysis Set**

	Vaccine	N*	Pre-vaccination		1 month post-vaccination		
			$\geq 0.1$ IU/mL (95% CI)	$\geq 1.0$ IU/mL (95% CI)	$\geq 0.1$ IU/mL (95% CI) <sup>†</sup>	$\geq 1.0$ IU/mL (95% CI) <sup>††</sup>	%Booster <sup>†††</sup> (95% CI)
Anti-Tetanus Toxoid (ELISA - IU/mL)	Adacel	944-948	97.2 (96.0; 98.2)	62.3 (59.1; 65.4)	100.0 (99.6; 100.0)	99.9 (99.4; 100.0)	74.5 <sup>§‡</sup> (71.6; 77.2)
	Td** Adsorbed	315-317	96.5 (93.8; 98.2)	63.8 (58.2; 69.1)	100.0 (98.8; 100.0)	100.0 (98.8; 100.0)	81.6 <sup>§‡</sup> (76.9; 85.7)
Anti-Diphtheria Toxin (ELISA - IU/mL)	Adacel	945-948	84.7 (82.2; 86.9)	29.1 (26.2; 32.1)	99.8 (99.2; 100.0)	94.9 (93.3; 96.2)	83.2 <sup>§</sup> (80.6; 85.5)
	Td** Adsorbed	315-317	83.8 (79.3; 87.7)	29.8 (24.8; 35.2)	99.4 (97.7; 99.9)	94.0 (90.8; 96.4)	84.1 <sup>§</sup> (79.6; 88.0)

\* N = number of participants in the per-protocol population with available data.

\*\* Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur Limited, Toronto, Ontario, Canada.

<sup>†</sup> Seroprotection rates at  $\geq 0.10$  IU/mL for Adacel were non-inferior to Td for diphtheria toxin and tetanus toxoid (upper limit of the 95% CI on the difference for Td vaccine minus Adacel  $< 10\%$ ).

<sup>††</sup> Seroprotection rates at  $\geq 1.0$  IU/mL were not prospectively defined as a primary or secondary endpoint.

<sup>†††</sup> Booster response is defined as a minimum rise in antibody concentration from pre to post-vaccination. The minimum rise is at least 2 times if the pre-vaccination concentration is above the cutoff value, or at least 4 times if it is at or below the cutoff value. The cutoff values for tetanus and diphtheria are 2.7 IU/mL and 2.56 IU/mL, respectively.

<sup>§</sup> n/M: defines the number n of participants with booster response / the number M of subjects with available data to evaluate booster response. There were (n/M) 703/944, 257/315, 786/945 and 265/315 for Adacel/Tetanus, Td Adsorbed/Tetanus, Adacel/Diphtheria, and Td Adsorbed/Diphtheria, respectively.

<sup>‡</sup> Booster response rates for tetanus toxoid in Adacel did not meet the pre-specified non-inferiority criteria.

For all pertussis antigens (PT, FHA, PRN and FIM), post-vaccination anti-pertussis GMCs in the Adacel group were non-inferior to GMCs induced by 3 or 4 doses of DAPTACEL in historical studies as are presented in [Table 9](#).

**Table 9: Ratio of Pertussis Antibody Geometric Mean Concentrations (GMCs) Observed One Month Following a Second Vaccination with Adacel in Adults Compared with Those Observed in Infants One Month following Vaccination with 3 or 4 Doses of DAPTACEL (Per-Protocol Analysis Set)**

Antigen	N	Adacel		N	DAPTACEL*		Adacel/DAPTACEL*	
		GMC (EU/mL)	(95% CI)		GMC (EU/mL)	(95% CI)	GMC Ratio	(95% CI) <sup>†</sup>
PT	935	102	(94.9; 110)	366	98.1	(90.9; 106)	1.04	(0.92; 1.18)
FHA	948	209	(200; 217)	80	39.9	(34.6; 46.1)	5.22	(4.51; 6.05)
PRN	948	318	(302; 334)	80	108	(91.4; 128)	2.94	(2.46; 3.51)
FIM	948	745	(711; 781)	80	341	(270; 431)	2.18	(1.84; 2.60)

- \* DAPTACEL: Historical controls who received DAPTACEL in Sanofi Pasteur studies. PT antibody GMC were compared to GMC following 4 doses of DAPTACEL in M5A10. FHA, PRN and FIM antibody GMCs were compared to GMCs following 3 doses of Daptacel in the Sweden I Efficacy trial.
- † For each pertussis antigen, non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the GMC ratio (Adacel divided by the historical control) was > 0.66.

Booster response rates for PT and FHA were non-inferior in Adacel participants compared to pre-specified criteria for booster response rates, but non-inferiority was not achieved for PRN and FIM booster response rates (See Table 10).

**Table 10: Comparison of Booster Response\* Rates for Pertussis Antigens Following a Second Vaccination with Adacel (Per-Protocol Analysis Set)**

	Adacel (N=948)		Pre-specified criteria for Booster Response Rates†	Adacel minus Pre-specified Booster Response Rates‡	
Antigen	n/M	% (95% CI)	%	Difference (%)	(95% CI)*
PT	693/894	77.5 (74.6; 80.2)	61.4	16.12	(13.27; 18.73)
FHA	651/945	68.9 (65.8; 71.8)	73.1	-4.21	(-7.23; -1.34)
PRN	617/945	65.3 (62.2; 68.3)	83.9	-18.61	(-21.7; -15.6)
FIM	537/945	56.8 (53.6; 60.0)	75.9	-19.07	(-22.3; -16.0)

- \* Booster response is defined as a minimum rise in antibody concentration from pre to post-vaccination. The minimum rise is at least 2-fold if the pre-vaccination concentration is above the cutoff value, or at least 4-fold if it is at or below the cutoff value. The cutoff values for Study Td537 for the pertussis antigens are: 93 EU/mL for PT, 170 EU/mL for FHA, 115 EU/mL for PRN, and 285 EU/mL for FIM.

N= number of subjects analyzed according to Per-Protocol Analysis Set

M=number of subjects with available data for the considered endpoint

n= number of subjects fulfilling the item listed in the first column

† Pre-specified criteria for booster response rates were derived from participants 21 to <65 years of age who received Adacel in Study Td506.

‡ Non-inferiority in booster response rate for each pertussis antigen was demonstrated if the lower limit of the 2-sided 95% CI of the difference of booster response rates between participants receiving Adacel in Study Td537 and expected booster response rates based on Study Td506 was >-10%.

### 14.3 Concomitant Hepatitis B Vaccine Administration

The concomitant use of Adacel (first vaccination) and hepatitis B (Hep B) vaccine (Recombivax HB®, 10 mcg per dose using a two-dose regimen, manufactured by Merck and Co., Inc.) was evaluated in a multi-center, open-labeled, randomized, controlled study that enrolled 410 adolescents, 11 through 14 years of age inclusive. One group received Adacel and Hep B vaccines concurrently (N = 206). The other group (N = 204) received Adacel at the first visit, then 4-6 weeks later received Hep B vaccine. The second dose of Hep B vaccine was given 4-6 weeks after the first dose. Serum samples were obtained prior to and 4-6 weeks after Adacel administration, as well as 4-6 weeks after the 2<sup>nd</sup> dose of Hep B for all participants. No interference was observed in the immune responses to any of the vaccine antigens when Adacel and Hep B vaccines were given concurrently or separately. [See *ADVERSE REACTIONS* (6.1).]



#### 14.4 Concomitant Influenza Vaccine Administration

The concomitant use of Adacel (first vaccination) and trivalent inactivated influenza vaccine (TIV, Fluzone<sup>®</sup>, manufactured by Sanofi Pasteur Inc., Swiftwater, PA) was evaluated in a multi-center, open-labeled, randomized, controlled study conducted in 720 adults, 19-64 years of age inclusive. In one group, participants received Adacel and TIV vaccines concurrently (N = 359). The other group received TIV at the first visit, then 4-6 weeks later received Adacel (N = 361). Sera were obtained prior to and 4-6 weeks after Adacel, as well as 4-6 weeks after the TIV. The immune responses were comparable for concurrent and separate administration of Adacel and TIV vaccines for diphtheria (percent of participants with seroprotective concentration  $\geq 0.10$  IU/mL and booster responses), tetanus (percent of participants with seroprotective concentration  $\geq 0.10$  IU/mL), pertussis antigens (booster responses and GMCs except lower PRN GMC in the concomitant group, lower bound of the 90% CI was 0.61 and the prespecified criterion was  $\geq 0.67$ ) and influenza antigens (percent of participants with hemagglutination-inhibition [HI] antibody titer  $\geq 1:40$  IU/mL and  $\geq 4$ -fold rise in HI titer). Although tetanus booster response rates were significantly lower in the group receiving the vaccines concurrently versus separately, greater than 98% of participants in both groups achieved seroprotective levels of  $\geq 0.1$  IU/mL. [See *ADVERSE REACTIONS* (6.1).]



## 15 REFERENCES

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- 8 Gustafsson L, et al. A controlled trial of a two-component acellular, a five-component acellular and a whole-cell pertussis vaccine. N Engl J Med 1996;334(6):349-55.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

Syringe, without needle, 1 dose – NDC 49281-400-89 (not made with natural rubber latex); in package of 5 syringes, NDC 49281-400-20

Syringe, without needle, 1 dose – NDC 49281-400-88; in package of 5 syringes, NDC 49281-400-15. The tip caps of the prefilled syringes may contain natural rubber latex. No other components are made with natural rubber latex.

Vial, 1 dose – NDC 49281-400-58; in package of 5 vials; NDC 49281-400-05. The vial stopper is not made with natural rubber latex.

Vial, 1 dose – NDC 49281-400-58; in package of 10 vials; NDC 49281-400-10. The vial stopper is not made with natural rubber latex.

Not all pack sizes may be marketed.

Adacel should be stored at 2°C to 8°C (35°F to 46°F). DO NOT FREEZE. Product which has been exposed to freezing should not be used. Do not use after expiration date shown on the label.

## **17 PATIENT COUNSELING INFORMATION**

Before administration of Adacel, healthcare providers should inform the patient, parent or guardian of the benefits and risks of the vaccine and the importance of receiving recommended booster dose unless a contraindication to further immunization exists.

The healthcare provider should inform the patient, parent or guardian about the potential for adverse reactions that have been temporally associated with Adacel or other vaccines containing similar components. The healthcare provider should provide the Vaccine Information Statements (VISs) that are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The patient, parent or guardian should be instructed to report any serious adverse reactions to their healthcare provider.

### **Pregnancy Exposure Registry**

[See *USE IN SPECIFIC POPULATIONS (8.1)*.]

Manufactured by:  
**Sanofi Pasteur Limited**  
Toronto Ontario Canada

Distributed by:  
**Sanofi Pasteur Inc.**  
Swiftwater PA 18370 USA

Adacel<sup>®</sup> is a registered trademark of Sanofi, its affiliates, and its subsidiaries.

R11-0119 USA

SANOFI PASTEUR 

# **EXHIBIT 257**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use GARDASIL safely and effectively. See full prescribing information for GARDASIL.

**GARDASIL®**

[Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]

Suspension for intramuscular injection

Initial U.S. Approval: 2006

**INDICATIONS AND USAGE**

GARDASIL is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine:

- Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18 (1.1)
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11 (1.1)

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS) (1.1)
- Cervical intraepithelial neoplasia (CIN) grade 1 (1.1)
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3 (1.1)
- Vaginal intraepithelial neoplasia (ValN) grade 2 and grade 3 (1.1)
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 (1.1)

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:

- Anal cancer caused by HPV types 16 and 18 (1.2)
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11 (1.2)

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. (1.2)

Limitations of GARDASIL Use and Effectiveness:

- GARDASIL does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. (1.3, 17)
- Recipients of GARDASIL should not discontinue anal cancer screening if it has been recommended by a health care provider. (1.3, 17)
- GARDASIL has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity. (1.3, 14.4, 14.5)
- GARDASIL is not intended to be used for treatment of active external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; ValN, or AIN. (1.3)
- GARDASIL has not been demonstrated to protect against diseases due to HPV types not contained in the vaccine. (1.3, 14.4, 14.5)

- Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL protects only against those vulvar, vaginal, and anal cancers caused by HPV 16 and 18. (1.3)
- GARDASIL does not protect against genital diseases not caused by HPV. (1.3)
- Vaccination with GARDASIL may not result in protection in all vaccine recipients. (1.3)
- GARDASIL has not been demonstrated to prevent HPV-related CIN 2/3 or worse in women older than 26 years of age. (14.7)

**DOSAGE AND ADMINISTRATION**

0.5-mL suspension for intramuscular injection at the following schedule: 0, 2 months, 6 months. (2.1)

**DOSAGE FORMS AND STRENGTHS**

- 0.5-mL suspension for injection as a single-dose vial and prefilled syringe. (3, 11)

**CONTRAINDICATIONS**

- Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL. (4, 11)

**WARNINGS AND PRECAUTIONS**

- Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with GARDASIL. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. (5.1)

**ADVERSE REACTIONS**

The most common adverse reaction was headache. Common adverse reactions (frequency of at least 1.0% and greater than AAHS control or saline placebo) are fever, nausea, dizziness; and injection-site pain, swelling, erythema, pruritus, and bruising. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

**DRUG INTERACTIONS**

GARDASIL may be administered concomitantly with RECOMBIVAX HB® (7.1) or with Menactra and Adacel. (7.2)

**USE IN SPECIFIC POPULATIONS**

Safety and effectiveness of GARDASIL have not been established in the following populations:

- Pregnant women. Women who receive GARDASIL during pregnancy are encouraged to contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231. (8.1)
- Children below the age of 9 years. (8.4)
- Immunocompromised individuals. Response to GARDASIL may be diminished. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2015

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**16 HOW SUPPLIED/STORAGE AND HANDLING****17 PATIENT COUNSELING INFORMATION**

\*Sections or subsections omitted from the full prescribing information are not listed.

**FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE****1.1 Girls and Women**

GARDASIL® is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine:

- Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

**1.2 Boys and Men**

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:

- Anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

**1.3 Limitations of GARDASIL Use and Effectiveness**

The health care provider should inform the patient, parent, or guardian that vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL should continue to undergo cervical cancer screening per standard of care. [See *Patient Counseling Information* (17).]

Recipients of GARDASIL should not discontinue anal cancer screening if it has been recommended by a health care provider. [See *Patient Counseling Information* (17).]

GARDASIL has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity. [See *Clinical Studies* (14.4, 14.5).]

GARDASIL is not intended to be used for treatment of active external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; VaIN; or AIN.

GARDASIL has not been demonstrated to protect against diseases due to HPV types not contained in the vaccine. [See *Clinical Studies* (14.4, 14.5).]

Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL protects only against those vulvar, vaginal, and anal cancers caused by HPV 16 and 18.

GARDASIL does not protect against genital diseases not caused by HPV.

Vaccination with GARDASIL may not result in protection in all vaccine recipients.

GARDASIL has not been demonstrated to prevent HPV-related CIN 2/3 or worse in women older than 26 years of age. [See *Clinical Studies* (14.7).]

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Dosage**

GARDASIL should be administered intramuscularly as a 0.5-mL dose at the following schedule: 0, 2 months, 6 months. [See *Clinical Studies* (14.8).]

### **2.2 Method of Administration**

For intramuscular use only.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine. GARDASIL should not be diluted or mixed with other vaccines. After thorough agitation, GARDASIL is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the product if particulates are present or if it appears discolored.

GARDASIL should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

Syncope has been reported following vaccination with GARDASIL and may result in falling with injury; observation for 15 minutes after administration is recommended. [See *Warnings and Precautions* (5.1).]

#### **Single-Dose Vial Use**

Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe and use promptly.

#### **Prefilled Syringe Use**

This package does not contain a needle. Shake well before use. Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol.

## **3 DOSAGE FORMS AND STRENGTHS**

GARDASIL is a suspension for intramuscular administration available in 0.5-mL single dose vials and prefilled syringes. See *Description* (11) for the complete listing of ingredients.

## **4 CONTRAINDICATIONS**

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL. [See *Description* (11).]

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Syncope**

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with GARDASIL. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

### **5.2 Managing Allergic Reactions**

Appropriate medical treatment and supervision must be readily available in case of anaphylactic reactions following the administration of GARDASIL.

## **6 ADVERSE REACTIONS**

### **Overall Summary of Adverse Reactions**

Headache, fever, nausea, and dizziness; and local injection site reactions (pain, swelling, erythema, pruritus, and bruising) occurred after administration with GARDASIL.

Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with GARDASIL and may result in falling with injury; observation for 15 minutes after administration is recommended. [See *Warnings and Precautions* (5.1).]

Anaphylaxis has been reported following vaccination with GARDASIL.



## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

### *Studies in Girls and Women (9 Through 45 Years of Age) and Boys and Men (9 Through 26 Years of Age)*

In 7 clinical trials (5 Amorphous Aluminum Hydroxyphosphate Sulfate [AAHS]-controlled, 1 saline placebo-controlled, and 1 uncontrolled), 18,083 individuals were administered GARDASIL or AAHS control or saline placebo on the day of enrollment, and approximately 2 and 6 months thereafter, and safety was evaluated using vaccination report cards (VRC)-aided surveillance for 14 days after each injection of GARDASIL or AAHS control or saline placebo in these individuals. The individuals who were monitored using VRC-aided surveillance included 10,088 individuals 9 through 45 years of age at enrollment who received GARDASIL and 7,995 individuals who received AAHS control or saline placebo. Few individuals (0.2%) discontinued due to adverse reactions. The race distribution of the 9- through 26-year-old girls and women in the safety population was as follows: 62.3% White; 17.6% Hispanic (Black and White); 6.8% Asian; 6.7% Other; 6.4% Black; and 0.3% American Indian. The race distribution of the 24- through 45-year-old women in the safety population of Study 6 was as follows: 20.6% White; 43.2% Hispanic (Black and White); 0.2% Other; 4.8% Black; 31.2% Asian; and 0.1% American Indian. The race distribution of the 9- through 26-year-old boys and men in the safety population was as follows: 42.0% White; 19.7% Hispanic (Black and White); 11.0% Asian; 11.2% Other; 15.9% Black; and 0.1% American Indian.

### *Common Injection-Site Adverse Reactions in Girls and Women 9 Through 26 Years of Age*

The injection site adverse reactions that were observed among recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients are shown in Table 1.

**Table 1: Injection-Site Adverse Reactions in Girls and Women 9 Through 26 Years of Age\***

<b>Adverse Reaction</b> (1 to 5 Days Postvaccination)	<b>GARDASIL</b> (N = 5088) %	<b>AAHS Control<sup>†</sup></b> (N = 3470) %	<b>Saline Placebo</b> (N = 320) %
<i>Injection Site</i>			
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.7	18.4	12.1
Pruritus	3.2	2.8	0.6
Bruising	2.8	3.2	1.6

\*The injection-site adverse reactions that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients.

<sup>†</sup>AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

### *Common Injection-Site Adverse Reactions in Boys and Men 9 Through 26 Years of Age*

The injection site adverse reactions that were observed among recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients are shown in Table 2.

**Table 2: Injection-Site Adverse Reactions in Boys and Men 9 Through 26 Years of Age\***

<b>Adverse Reaction</b> (1 to 5 Days Postvaccination)	<b>GARDASIL</b> (N = 3093) %	<b>AAHS Control<sup>†</sup></b> (N = 2029) %	<b>Saline Placebo</b> (N = 274) %
<i>Injection Site</i>			
Pain	61.4	50.8	41.6
Erythema	16.7	14.1	14.5
Swelling	13.9	9.6	8.2
Hematoma	1.0	0.3	3.3

\*The injection-site adverse reactions that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients.

†AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

#### *Evaluation of Injection-Site Adverse Reactions by Dose in Girls and Women 9 Through 26 Years of Age*

An analysis of injection-site adverse reactions in girls and women by dose is shown in Table 3. Of those girls and women who reported an injection-site reaction, 94.3% judged their injection-site adverse reaction to be mild or moderate in intensity.

**Table 3: Postdose Evaluation of Injection-Site Adverse Reactions in Girls and Women 9 Through 26 Years of Age (1 to 5 Days Postvaccination)**

	GARDASIL (% occurrence)			AAHS Control* (% occurrence)			Saline Placebo (% occurrence)		
Adverse Reaction	Post-dose 1 N <sup>†</sup> = 5011	Post-dose 2 N = 4924	Post-dose 3 N = 4818	Post-dose 1 N = 3410	Post-dose 2 N = 3351	Post-dose 3 N = 3295	Post-dose 1 N = 315	Post-dose 2 N = 301	Post-dose 3 N = 300
<b>Pain</b>	63.4	60.7	62.7	57.0	47.8	49.6	33.7	20.3	27.3
Mild/Moderate	62.5	59.7	61.2	56.6	47.3	48.9	33.3	20.3	27.0
Severe	0.9	1.0	1.5	0.4	0.5	0.6	0.3	0.0	0.3
<b>Swelling<sup>‡</sup></b>	10.2	12.8	15.1	8.2	7.5	7.6	4.4	3.0	3.3
Mild/Moderate	9.6	11.9	14.2	8.1	7.2	7.3	4.4	3.0	3.3
Severe	0.6	0.8	0.9	0.2	0.2	0.2	0.0	0.0	0.0
<b>Erythema<sup>‡</sup></b>	9.2	12.1	14.7	9.8	8.4	8.9	7.3	5.3	5.7
Mild/Moderate	9.0	11.7	14.3	9.5	8.4	8.8	7.3	5.3	5.7
Severe	0.2	0.3	0.4	0.3	0.1	0.1	0.0	0.0	0.0

\*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

†N = Number of individuals with follow-up

‡Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

#### *Evaluation of Injection-Site Adverse Reactions by Dose in Boys and Men 9 Through 26 Years of Age*

An analysis of injection-site adverse reactions in boys and men by dose is shown in Table 4. Of those boys and men who reported an injection-site reaction, 96.4% judged their injection-site adverse reaction to be mild or moderate in intensity.

**Table 4: Postdose Evaluation of Injection-Site Adverse Reactions in Boys and Men 9 Through 26 Years of Age (1 to 5 Days Postvaccination)**

	GARDASIL (% occurrence)			AAHS Control* (% occurrence)			Saline Placebo (% occurrence)		
Adverse Reaction	Post-dose 1 N <sup>†</sup> = 3003	Post-dose 2 N = 2898	Post-dose 3 N = 2826	Post-dose 1 N = 1950	Post-dose 2 N = 1854	Post-dose 3 N = 1799	Post-dose 1 N = 269	Post-dose 2 N = 263	Post-dose 3 N = 259
<b>Pain</b>	44.7	36.9	34.4	38.4	28.2	25.8	27.5	20.5	16.2
Mild/Moderate	44.5	36.4	34.1	37.9	28.2	25.5	27.5	20.2	16.2
Severe	0.2	0.5	0.3	0.4	0.1	0.3	0.0	0.4	0.0
<b>Swelling<sup>‡</sup></b>	5.6	6.6	7.7	5.6	4.5	4.1	4.8	1.5	3.5
Mild/Moderate	5.3	6.2	7.1	5.4	4.5	4.0	4.8	1.5	3.1
Severe	0.2	0.3	0.5	0.2	0.0	0.1	0.0	0.0	0.4
<b>Erythema<sup>‡</sup></b>	7.2	8.0	8.7	8.3	6.3	5.7	7.1	5.7	5.0
Mild/Moderate	6.8	7.7	8.3	8.0	6.2	5.6	7.1	5.7	5.0
Severe	0.3	0.2	0.3	0.2	0.1	0.1	0.0	0.0	0.0

\*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

†N = Number of individuals with follow-up

‡Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

#### *Common Systemic Adverse Reactions in Girls and Women 9 Through 26 Years of Age*

Headache was the most commonly reported systemic adverse reaction in both treatment groups (GARDASIL = 28.2% and AAHS control or saline placebo = 28.4%). Fever was the next most commonly

reported systemic adverse reaction in both treatment groups (GARDASIL = 13.0% and AAHS control or saline placebo = 11.2%).

Adverse reactions that were observed among recipients of GARDASIL, at a frequency of greater than or equal to 1.0% where the incidence in the GARDASIL group was greater than or equal to the incidence in the AAHS control or saline placebo group, are shown in Table 5.

**Table 5: Common Systemic Adverse Reactions in Girls and Women 9 Through 26 Years of Age (GARDASIL ≥ Control)\***

<b>Adverse Reactions</b> (1 to 15 Days Postvaccination)	<b>GARDASIL</b> (N = 5088) %	<b>AAHS Control<sup>†</sup> or Saline Placebo</b> (N = 3790) %
Pyrexia	13.0	11.2
Nausea	6.7	6.5
Dizziness	4.0	3.7
Diarrhea	3.6	3.5
Vomiting	2.4	1.9
Cough	2.0	1.5
Toothache	1.5	1.4
Upper respiratory tract infection	1.5	1.5
Malaise	1.4	1.2
Arthralgia	1.2	0.9
Insomnia	1.2	0.9
Nasal congestion	1.1	0.9

\*The adverse reactions in this table are those that were observed among recipients of GARDASIL at a frequency of at least 1.0% and greater than or equal to those observed among AAHS control or saline placebo recipients.

<sup>†</sup>AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

#### *Common Systemic Adverse Reactions in Boys and Men 9 Through 26 Years of Age*

Headache was the most commonly reported systemic adverse reaction in both treatment groups (GARDASIL = 12.3% and AAHS control or saline placebo = 11.2%). Fever was the next most commonly reported systemic adverse reaction in both treatment groups (GARDASIL = 8.3% and AAHS control or saline placebo = 6.5%).

Adverse reactions that were observed among recipients of GARDASIL, at a frequency of greater than or equal to 1.0% where the incidence in the group that received GARDASIL was greater than or equal to the incidence in the AAHS control or saline placebo group, are shown in Table 6.

**Table 6: Common Systemic Adverse Reactions in Boys and Men 9 Through 26 Years of Age (GARDASIL ≥ Control)\***

<b>Adverse Reactions</b> (1 to 15 Days Postvaccination)	<b>GARDASIL</b> (N = 3093) %	<b>AAHS Control<sup>†</sup> or Saline Placebo</b> (N = 2303) %
Headache	12.3	11.2
Pyrexia	8.3	6.5
Oropharyngeal pain	2.8	2.1
Diarrhea	2.7	2.2
Nasopharyngitis	2.6	2.6
Nausea	2.0	1.0
Upper respiratory tract infection	1.5	1.0
Abdominal pain upper	1.4	1.4
Myalgia	1.3	0.7
Dizziness	1.2	0.9
Vomiting	1.0	0.8

\*The adverse reactions in this table are those that were observed among recipients of GARDASIL at a frequency of at least 1.0% and greater than or equal to those observed among AAHS control or saline placebo recipients.

<sup>†</sup>AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

#### *Evaluation of Fever by Dose in Girls and Women 9 Through 26 Years of Age*

An analysis of fever in girls and women by dose is shown in Table 7.

**Table 7: Postdose Evaluation of Fever in Girls and Women 9 Through 26 Years of Age  
(1 to 5 Days Postvaccination)**

	GARDASIL (% occurrence)			AAHS Control* or Saline Placebo (% occurrence)		
Temperature (°F)	Postdose 1 N <sup>†</sup> = 4945	Postdose 2 N = 4804	Postdose 3 N = 4671	Postdose 1 N = 3681	Postdose 2 N = 3564	Postdose 3 N = 3467
≥100 to <102	3.7	4.1	4.4	3.1	3.8	3.6
≥102	0.3	0.5	0.5	0.2	0.4	0.5

\*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

<sup>†</sup>N = Number of individuals with follow-up**Evaluation of Fever by Dose in Boys and Men 9 Through 26 Years of Age**

An analysis of fever in boys and men by dose is shown in Table 8.

**Table 8: Postdose Evaluation of Fever in Boys and Men 9 Through 26 Years of Age  
(1 to 5 Days Postvaccination)**

	GARDASIL (% occurrence)			AAHS Control* or Saline Placebo (% occurrence)		
Temperature (°F)	Postdose 1 N <sup>†</sup> = 2972	Postdose 2 N = 2849	Postdose 3 N = 2792	Postdose 1 N = 2194	Postdose 2 N = 2079	Postdose 3 N = 2046
≥100 to <102	2.4	2.5	2.3	2.1	2.2	1.6
≥102	0.6	0.5	0.5	0.5	0.3	0.3

\*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

<sup>†</sup>N = Number of individuals with follow-up**Serious Adverse Reactions in the Entire Study Population**

Across the clinical studies, 258 individuals (GARDASIL N = 128 or 0.8%; placebo N = 130 or 1.0%) out of 29,323 (GARDASIL N = 15,706; AAHS control N = 13,023; or saline placebo N = 594) individuals (9- through 45-year-old girls and women; and 9- through 26-year-old boys and men) reported a serious systemic adverse reaction.

Of the entire study population (29,323 individuals), 0.04% of the reported serious systemic adverse reactions were judged to be vaccine related by the study investigator. The most frequently (frequency of 4 cases or greater with either GARDASIL, AAHS control, saline placebo, or the total of all three) reported serious systemic adverse reactions, regardless of causality, were:

Headache [0.02% GARDASIL (3 cases) vs. 0.02% AAHS control (2 cases)],  
 Gastroenteritis [0.02% GARDASIL (3 cases) vs. 0.02% AAHS control (2 cases)],  
 Appendicitis [0.03% GARDASIL (5 cases) vs. 0.01% AAHS control (1 case)],  
 Pelvic inflammatory disease [0.02% GARDASIL (3 cases) vs. 0.03% AAHS control (4 cases)],  
 Urinary tract infection [0.01% GARDASIL (2 cases) vs. 0.02% AAHS control (2 cases)],  
 Pneumonia [0.01% GARDASIL (2 cases) vs. 0.02% AAHS control (2 cases)],  
 Pyelonephritis [0.01% GARDASIL (2 cases) vs. 0.02% AAHS control (3 cases)],  
 Pulmonary embolism [0.01% GARDASIL (2 cases) vs. 0.02% AAHS control (2 cases)].

One case (0.006% GARDASIL; 0.0% AAHS control or saline placebo) of bronchospasm; and 2 cases (0.01% GARDASIL; 0.0% AAHS control or saline placebo) of asthma were reported as serious systemic adverse reactions that occurred following any vaccination visit.

In addition, there was 1 individual in the clinical trials, in the group that received GARDASIL, who reported two injection-site serious adverse reactions (injection-site pain and injection-site joint movement impairment).

**Deaths in the Entire Study Population**

Across the clinical studies, 40 deaths (GARDASIL N = 21 or 0.1%; placebo N = 19 or 0.1%) were reported in 29,323 (GARDASIL N = 15,706; AAHS control N = 13,023, saline placebo N = 594) individuals (9- through 45-year-old girls and women; and 9- through 26-year-old boys and men). The events reported were consistent with events expected in healthy adolescent and adult populations. The most common cause of death was motor vehicle accident (5 individuals who received GARDASIL and 4 individuals who received AAHS control), followed by drug overdose/suicide (2 individuals who received GARDASIL and 6 individuals who received AAHS control), gunshot wound (1 individual who received GARDASIL and 3 individuals who received AAHS control), and pulmonary embolus/deep vein thrombosis (1 individual who

received GARDASIL and 1 individual who received AAHS control). In addition, there were 2 cases of sepsis, 1 case of pancreatic cancer, 1 case of arrhythmia, 1 case of pulmonary tuberculosis, 1 case of hyperthyroidism, 1 case of post-operative pulmonary embolism and acute renal failure, 1 case of traumatic brain injury/cardiac arrest, 1 case of systemic lupus erythematosus, 1 case of cerebrovascular accident, 1 case of breast cancer, and 1 case of nasopharyngeal cancer in the group that received GARDASIL; 1 case of asphyxia, 1 case of acute lymphocytic leukemia, 1 case of chemical poisoning, and 1 case of myocardial ischemia in the AAHS control group; and 1 case of medulloblastoma in the saline placebo group.

#### *Systemic Autoimmune Disorders in Girls and Women 9 Through 26 Years of Age*

In the clinical studies, 9- through 26-year-old girls and women were evaluated for new medical conditions that occurred over the course of follow-up. New medical conditions potentially indicative of a systemic autoimmune disorder seen in the group that received GARDASIL or AAHS control or saline placebo are shown in Table 9. This population includes all girls and women who received at least one dose of GARDASIL or AAHS control or saline placebo, and had safety data available.

**Table 9: Summary of Girls and Women 9 Through 26 Years of Age Who Reported an Incident Condition Potentially Indicative of a Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL, Regardless of Causality**

Conditions	GARDASIL (N = 10,706)	AAHS Control* or Saline Placebo (N = 9412)
	n (%)	n (%)
Arthralgia/Arthritis/Arthropathy <sup>†</sup>	120 (1.1)	98 (1.0)
Autoimmune Thyroiditis	4 (0.0)	1 (0.0)
Celiac Disease	10 (0.1)	6 (0.1)
Diabetes Mellitus Insulin-dependent	2 (0.0)	2 (0.0)
Erythema Nodosum	2 (0.0)	4 (0.0)
Hyperthyroidism <sup>‡</sup>	27 (0.3)	21 (0.2)
Hypothyroidism <sup>§</sup>	35 (0.3)	38 (0.4)
Inflammatory Bowel Disease <sup>¶</sup>	7 (0.1)	10 (0.1)
Multiple Sclerosis	2 (0.0)	4 (0.0)
Nephritis <sup>#</sup>	2 (0.0)	5 (0.1)
Optic Neuritis	2 (0.0)	0 (0.0)
Pigmentation Disorder <sup>Ⓟ</sup>	4 (0.0)	3 (0.0)
Psoriasis <sup>Ⓠ</sup>	13 (0.1)	15 (0.2)
Raynaud's Phenomenon	3 (0.0)	4 (0.0)
Rheumatoid Arthritis <sup>Ⓡ</sup>	6 (0.1)	2 (0.0)
Scleroderma/Morphea	2 (0.0)	1 (0.0)
Stevens-Johnson Syndrome	1 (0.0)	0 (0.0)
Systemic Lupus Erythematosus	1 (0.0)	3 (0.0)
Uveitis	3 (0.0)	1 (0.0)
<b>All Conditions</b>	<b>245 (2.3)</b>	<b>218 (2.3)</b>

\*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

<sup>†</sup>Arthralgia/Arthritis/Arthropathy includes the following terms: Arthralgia, Arthritis, Arthritis reactive, and Arthropathy

<sup>‡</sup>Hyperthyroidism includes the following terms: Basedow's disease, Goiter, Toxic nodular goiter, and Hyperthyroidism

<sup>§</sup>Hypothyroidism includes the following terms: Hypothyroidism and thyroiditis

<sup>¶</sup>Inflammatory bowel disease includes the following terms: Colitis ulcerative, Crohn's disease, and Inflammatory bowel disease

<sup>#</sup>Nephritis includes the following terms: Nephritis, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative

<sup>Ⓟ</sup>Pigmentation disorder includes the following terms: Pigmentation disorder, Skin depigmentation, and Vitiligo

<sup>Ⓠ</sup>Psoriasis includes the following terms: Psoriasis, Pustular psoriasis, and Psoriatic arthropathy

<sup>Ⓡ</sup>Rheumatoid arthritis includes juvenile rheumatoid arthritis. One woman counted in the rheumatoid arthritis group reported rheumatoid arthritis as an adverse experience at Day 130.

N = Number of individuals enrolled

n = Number of individuals with specific new Medical Conditions

NOTE: Although an individual may have had two or more new Medical Conditions, the individual is counted only once within a category. The same individual may appear in different categories.

#### *Systemic Autoimmune Disorders in Boys and Men 9 Through 26 Years of Age*

In the clinical studies, 9- through 26-year-old boys and men were evaluated for new medical conditions that occurred over the course of follow-up. New medical conditions potentially indicative of a systemic autoimmune disorder seen in the group that received GARDASIL or AAHS control or saline placebo are

shown in Table 10. This population includes all boys and men who received at least one dose of GARDASIL or AAHS control or saline placebo, and had safety data available.

**Table 10: Summary of Boys and Men 9 Through 26 Years of Age Who Reported an Incident Condition Potentially Indicative of a Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL, Regardless of Causality**

Conditions	GARDASIL (N = 3093)	AAHS Control* or Saline Placebo (N = 2303)
	n (%)	n (%)
Alopecia Areata	2 (0.1)	0 (0.0)
Ankylosing Spondylitis	1 (0.0)	2 (0.1)
Arthralgia/Arthritis/Reactive Arthritis	30 (1.0)	17 (0.7)
Autoimmune Thrombocytopenia	1 (0.0)	0 (0.0)
Diabetes Mellitus Type 1	3 (0.1)	2 (0.1)
Hyperthyroidism	0 (0.0)	1 (0.0)
Hypothyroidism <sup>†</sup>	3 (0.1)	0 (0.0)
Inflammatory Bowel Disease <sup>‡</sup>	1 (0.0)	2 (0.1)
Myocarditis	1 (0.0)	1 (0.0)
Proteinuria	1 (0.0)	0 (0.0)
Psoriasis	0 (0.0)	4 (0.2)
Skin Depigmentation	1 (0.0)	0 (0.0)
Vitiligo	2 (0.1)	5 (0.2)
<b>All Conditions</b>	<b>46 (1.5)</b>	<b>34 (1.5)</b>

\*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

<sup>†</sup>Hypothyroidism includes the following terms: Hypothyroidism and Autoimmune thyroiditis

<sup>‡</sup>Inflammatory bowel disease includes the following terms: Colitis ulcerative and Crohn's disease

N = Number of individuals who received at least one dose of either vaccine or placebo

n = Number of individuals with specific new Medical Conditions

NOTE: Although an individual may have had two or more new Medical Conditions, the individual is counted only once within a category. The same individual may appear in different categories.

#### ***Safety in Concomitant Use with RECOMBIVAX HB<sup>®</sup> [hepatitis B vaccine (recombinant)] in Girls and Women 16 Through 23 Years of Age***

The safety of GARDASIL when administered concomitantly with RECOMBIVAX HB<sup>®</sup> [hepatitis B vaccine (recombinant)] was evaluated in an AAHS-controlled study of 1871 girls and women with a mean age of 20.4 years [see *Clinical Studies (14.10)*]. The race distribution of the study individuals was as follows: 61.6% White; 23.8% Other; 11.9% Black; 1.6% Hispanic (Black and White); 0.8% Asian; and 0.3% American Indian. The rates of systemic and injection-site adverse reactions were similar among girls and women who received concomitant vaccination as compared with those who received GARDASIL or RECOMBIVAX HB [hepatitis B vaccine (recombinant)].

#### ***Safety in Concomitant Use with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)]***

The safety of GARDASIL when administered concomitantly with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] was evaluated in a randomized study of 1040 boys and girls with a mean age of 12.6 years [see *Clinical Studies (14.11)*]. The race distribution of the study subjects was as follows: 77.7% White; 1.4% Multi-racial; 12.3% Black; 6.8% Hispanic (Black and White); 1.2% Asian; 0.4% American Indian, and 0.2% Indian.

There was an increase in injection-site swelling reported at the injection site for GARDASIL (concomitant = 10.9%, non-concomitant = 6.9%) when GARDASIL was administered concomitantly with Menactra and Adacel as compared to non-concomitant (separated by 1 month) vaccination. The majority of injection-site swelling adverse experiences were reported as being mild to moderate in intensity.

#### ***Safety in Women 27 Through 45 Years of Age***

The adverse reaction profile in women 27 through 45 years of age was comparable to the profile seen in girls and women 9 through 26 years of age.



## 6.2 Postmarketing Experience

The following adverse events have been spontaneously reported during post-approval use of GARDASIL. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

Blood and lymphatic system disorders: Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, lymphadenopathy.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolus.

Gastrointestinal disorders: Nausea, pancreatitis, vomiting.

General disorders and administration site conditions: Asthenia, chills, death, fatigue, malaise.

Immune system disorders: Autoimmune diseases, hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

Nervous system disorders: Acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, motor neuron disease, paralysis, seizures, syncope (including syncope associated with tonic-clonic movements and other seizure-like activity) sometimes resulting in falling with injury, transverse myelitis.

Infections and infestations: cellulitis.

Vascular disorders: Deep venous thrombosis.

## 7 DRUG INTERACTIONS

### 7.1 Use with RECOMBIVAX HB

Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site) with RECOMBIVAX HB [hepatitis B vaccine (recombinant)] [see *Clinical Studies* (14.10)].

### 7.2 Use with Menactra and Adacel

Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site) with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] [see *Clinical Studies* (14.11)].

### 7.3 Use with Hormonal Contraceptives

In clinical studies of 16- through 26-year-old women, 13,912 (GARDASIL N = 6952; AAHS control or saline placebo N = 6960) who had post-Month 7 follow-up used hormonal contraceptives for a total of 33,859 person-years (65.8% of the total follow-up time in the studies).

In one clinical study of 24- through 45-year-old women, 1357 (GARDASIL N = 690; AAHS control N = 667) who had post-Month 7 follow-up used hormonal contraceptives for a total of 3400 person-years (31.5% of the total follow-up time in the study). Use of hormonal contraceptives or lack of use of hormonal contraceptives among study participants did not impair the immune response in the per protocol immunogenicity (PPI) population.

### 7.4 Use with Systemic Immunosuppressive Medications

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines [see *Use in Specific Populations* (8.6)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Pregnancy Category B:*

Reproduction studies have been performed in female rats at doses equivalent to the recommended human dose and have revealed no evidence of impaired female fertility or harm to the fetus due to GARDASIL. There are, however, no adequate and well-controlled studies in pregnant women. Because



animal reproduction studies are not always predictive of human responses, GARDASIL should be used during pregnancy only if clearly needed.

An evaluation of the effect of GARDASIL on embryo-fetal, pre- and postweaning development was conducted using rats. One group of rats was administered GARDASIL twice prior to gestation, during the period of organogenesis (gestation Day 6) and on lactation Day 7. A second group of pregnant rats was administered GARDASIL during the period of organogenesis (gestation Day 6) and on lactation Day 7 only. GARDASIL was administered at 0.5 mL/rat/occasion (120 mcg total protein which is equivalent to the recommended human dose) by intramuscular injection. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-fetal or pre- and postweaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted in this study. In addition, there were no treatment-related effects on developmental signs, behavior, reproductive performance, or fertility of the offspring.

#### *Clinical Studies in Humans*

In clinical studies, women underwent urine pregnancy testing prior to administration of each dose of GARDASIL. Women who were found to be pregnant before completion of a 3-dose regimen of GARDASIL were instructed to defer completion of their vaccination regimen until resolution of the pregnancy.

GARDASIL is not indicated for women 27 years of age or older. However, safety data in women 16 through 45 years of age was collected, and 3819 women (GARDASIL N = 1894 vs. AAHS control or saline placebo N = 1925) reported at least 1 pregnancy each.

The overall proportions of pregnancies that resulted in an adverse outcome, defined as the combined numbers of spontaneous abortion, late fetal death, and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), were 22.6% (446/1973) in women who received GARDASIL and 23.1% (460/1994) in women who received AAHS control or saline placebo.

Overall, 55 and 65 women in the group that received GARDASIL or AAHS control or saline placebo, respectively (2.9% and 3.4% of all women who reported a pregnancy in the respective vaccination groups), experienced a serious adverse reaction during pregnancy. The most common events reported were conditions that can result in Cesarean section (e.g., failure of labor, malpresentation, cephalopelvic disproportion), premature onset of labor (e.g., threatened abortions, premature rupture of membranes), and pregnancy-related medical problems (e.g., pre-eclampsia, hyperemesis). The proportions of pregnant women who experienced such events were comparable between the groups receiving GARDASIL and AAHS control or saline placebo.

There were 45 cases of congenital anomaly in pregnancies that occurred in women who received GARDASIL and 34 cases of congenital anomaly in pregnancies that occurred in women who received AAHS control or saline placebo.

Further sub-analyses were conducted to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL or AAHS control or saline placebo. For pregnancies with estimated onset within 30 days of vaccination, 5 cases of congenital anomaly were observed in the group that received GARDASIL compared to 1 case of congenital anomaly in the group that received AAHS control or saline placebo. The congenital anomalies seen in pregnancies with estimated onset within 30 days of vaccination included pyloric stenosis, congenital megacolon, congenital hydronephrosis, hip dysplasia, and club foot. Conversely, in pregnancies with onset more than 30 days following vaccination, 40 cases of congenital anomaly were observed in the group that received GARDASIL compared with 33 cases of congenital anomaly in the group that received AAHS control or saline placebo.

**Women who receive GARDASIL during pregnancy are encouraged to contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).**

### **8.3 Nursing Mothers**

#### *Women 16 Through 45 Years of Age*

It is not known whether GARDASIL is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GARDASIL is administered to a nursing woman.

GARDASIL or AAHS control were given to a total of 1133 women (vaccine N = 582, AAHS control N = 551) during the relevant Phase 3 clinical studies.

Overall, 27 and 13 infants of women who received GARDASIL or AAHS control, respectively (representing 4.6% and 2.4% of the total number of women who were breast-feeding during the period in which they received GARDASIL or AAHS control, respectively), experienced a serious adverse reaction.

In a post-hoc analysis of clinical studies, a higher number of breast-feeding infants (n = 7) whose mothers received GARDASIL had acute respiratory illnesses within 30 days post vaccination of the mother as compared to infants (n = 2) whose mothers received AAHS control.

#### **8.4 Pediatric Use**

Safety and effectiveness have not been established in pediatric patients below 9 years of age.

#### **8.5 Geriatric Use**

The safety and effectiveness of GARDASIL have not been evaluated in a geriatric population, defined as individuals aged 65 years and over.

#### **8.6 Immunocompromised Individuals**

The immunologic response to GARDASIL may be diminished in immunocompromised individuals [see *Drug Interactions* (7.4)].

### **10 OVERDOSAGE**

There have been reports of administration of higher than recommended doses of GARDASIL.

In general, the adverse event profile reported with overdose was comparable to recommended single doses of GARDASIL.

### **11 DESCRIPTION**

GARDASIL, Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant, is a non-infectious recombinant quadrivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate). The quadrivalent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

GARDASIL is a sterile suspension for intramuscular administration. Each 0.5-mL dose contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein.

Each 0.5-mL dose of the vaccine contains approximately 225 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein/dose, and water for injection. The product does not contain a preservative or antibiotics.

After thorough agitation, GARDASIL is a white, cloudy liquid.

### **12 CLINICAL PHARMACOLOGY**

#### **12.1 Mechanism of Action**

HPV only infects human beings. Animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines may involve the development of humoral immune responses. Human beings develop a humoral immune response to the vaccine, although the exact mechanism of protection is unknown.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

GARDASIL has not been evaluated for the potential to cause carcinogenicity or genotoxicity.

GARDASIL administered to female rats at a dose of 120 mcg total protein, which is equivalent to the recommended human dose, had no effects on mating performance, fertility, or embryonic/fetal survival.

The effect of GARDASIL on male fertility has been studied in male rats at an intramuscular dose of 0.5 mL/rat/occasion (120 mcg total protein which is equivalent to the recommended human dose). One group of male rats was administered GARDASIL once, 3 days prior to cohabitation, and a second group of male rats was administered GARDASIL three times, at 6 weeks, 3 weeks, and 3 days prior to cohabitation. There were no treatment-related effects on reproductive performance including fertility, sperm count, and sperm motility. There were no treatment-related gross or histomorphologic and weight changes on the testes.

## 14 CLINICAL STUDIES

CIN 2/3 and AIS are the immediate and necessary precursors of squamous cell carcinoma and adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to prevent cancer; thus, they serve as surrogate markers for prevention of cervical cancer. In the clinical studies in girls and women aged 16 through 26 years, cases of CIN 2/3 and AIS were the efficacy endpoints to assess prevention of cervical cancer. In addition, cases of VIN 2/3 and VaIN 2/3 were the efficacy endpoints to assess prevention of HPV-related vulvar and vaginal cancers, and observations of external genital lesions were the efficacy endpoints for the prevention of genital warts.

In clinical studies in boys and men aged 16 through 26 years, efficacy was evaluated using the following endpoints: external genital warts and penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3 or penile/perineal/perianal cancer. In addition, cases of AIN grades 1/2/3 and anal cancer made up the composite efficacy endpoint used to assess prevention of HPV-related anal cancer.

Anal HPV infection, AIN, and anal cancer were not endpoints in the studies conducted in women. The similarity of HPV-related anal disease in men and women supports bridging the indication of prevention of AIN and anal cancer to women.

Efficacy was assessed in 6 AAHS-controlled, double-blind, randomized Phase 2 and 3 clinical studies. The first Phase 2 study evaluated the HPV 16 component of GARDASIL (Study 1, N = 2391 16- through 26-year-old girls and women) and the second evaluated all components of GARDASIL (Study 2, N = 551 16- through 26-year-old girls and women). Two Phase 3 studies evaluated GARDASIL in 5442 (Study 3) and 12,157 (Study 4) 16- through 26-year-old girls and women. A third Phase 3 study, Study 5, evaluated GARDASIL in 4055 16- through 26-year-old boys and men, including a subset of 598 (GARDASIL = 299; placebo = 299) men who self-identified as having sex with men (MSM population). A fourth Phase 3 study, Study 6, evaluated GARDASIL in 3817 24- through 45-year-old women. Together, these six studies evaluated 28,413 individuals (20,541 girls and women 16 through 26 years of age at enrollment with a mean age of 20.0 years, 4055 boys and men 16 through 26 years of age at enrollment with a mean age of 20.5 years, and 3817 women 24 through 45 years of age at enrollment with a mean age of 34.3 years). The race distribution of the 16- through 26-year-old girls and women in the clinical trials was as follows: 70.4% White; 12.2% Hispanic (Black and White); 8.8% Other; 4.6% Black; 3.8% Asian; and 0.2% American Indian. The race distribution of the 16- through 26-year-old boys and men in the clinical trials was as follows: 35.2% White; 20.5% Hispanic (Black and White); 14.4% Other; 19.8% Black; 10.0% Asian; and 0.1% American Indian. The race distribution of the 24- through 45-year-old women in the clinical trials was as follows: 20.6% White; 43.2% Hispanic (Black and White); 0.2% Other; 4.8% Black; 31.2% Asian; and 0.1% American Indian.

The median duration of follow-up was 4.0, 3.0, 3.0, 3.0, 2.3, and 4.0 years for Study 1, Study 2, Study 3, Study 4, Study 5, and Study 6, respectively. Individuals received vaccine or AAHS control on the day of enrollment and 2 and 6 months thereafter. Efficacy was analyzed for each study individually and for all studies in girls and women combined according to a prospective clinical plan.

Overall, 73% of 16- through 26-year-old girls and women, 67% of 24- through 45-year-old women, and 83% of 16- through 26-year-old boys and men were naïve (i.e., PCR [Polymerase Chain Reaction] negative and seronegative for all 4 vaccine HPV types) to all 4 vaccine HPV types at enrollment.

A total of 27% of 16- through 26-year-old girls and women, 33% of 24- through 45-year-old women, and 17% of 16- through 26-year-old boys and men had evidence of prior exposure to or ongoing infection with at least 1 of the 4 vaccine HPV types. Among these individuals, 74% of 16- through 26-year-old girls and women, 71% of 24- through 45-year-old women, and 78% of 16- through 26-year-old boys and men had evidence of prior exposure to or ongoing infection with only 1 of the 4 vaccine HPV types and were naïve (PCR negative and seronegative) to the remaining 3 types.

In 24- through 45-year-old individuals, 0.4% had been exposed to all 4 vaccine HPV types.

In individuals who were naïve (PCR negative and seronegative) to all 4 vaccine HPV types, CIN, genital warts, VIN, VaIN, PIN, and persistent infection caused by any of the 4 vaccine HPV types were counted as endpoints.

Among individuals who were positive (PCR positive and/or seropositive) for a vaccine HPV type at Day 1, endpoints related to that type were not included in the analyses of prophylactic efficacy. Endpoints related to the remaining types for which the individual was naïve (PCR negative and seronegative) were counted.

For example, in individuals who were HPV 18 positive (PCR positive and/or seropositive) at Day 1, lesions caused by HPV 18 were not counted in the prophylactic efficacy evaluations. Lesions caused by HPV 6, 11, and 16 were included in the prophylactic efficacy evaluations. The same approach was used for the other types.

#### **14.1 Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in Girls and Women 16 through 26 Years of Age**

GARDASIL was administered without prescreening for presence of HPV infection and the efficacy trials allowed enrollment of girls and women regardless of baseline HPV status (i.e., PCR status or serostatus). Girls and women with current or prior HPV infection with an HPV type contained in the vaccine were not eligible for prophylactic efficacy evaluations for that type.

The primary analyses of efficacy with respect to HPV types 6, 11, 16, and 18 were conducted in the per-protocol efficacy (PPE) population, consisting of girls and women who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative in cervicovaginal specimens and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7). Efficacy was measured starting after the Month 7 visit.

GARDASIL was efficacious in reducing the incidence of CIN (any grade including CIN 2/3); AIS; genital warts; VIN (any grade); and VaIN (any grade) related to vaccine HPV types 6, 11, 16, or 18 in those who were PCR negative and seronegative at baseline (Table 11).

In addition, girls and women who were already infected with 1 or more vaccine-related HPV types prior to vaccination were protected from precancerous cervical lesions and external genital lesions caused by the other vaccine HPV types.

**Table 11: Analysis of Efficacy of GARDASIL in the PPE\* Population† of 16- Through 26-Year-Old Girls and Women for Vaccine HPV Types**

Population	GARDASIL		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
HPV 16- or 18-related CIN 2/3 or AIS					
Study 1 <sup>‡</sup>	755	0	750	12	100.0 (65.1, 100.0)
Study 2	231	0	230	1	100.0 (-3744.9, 100.0)
Study 3	2201	0	2222	36	100.0 (89.2, 100.0)
Study 4	5306	2	5262	63	96.9 (88.2, 99.6)
Combined Protocols <sup>§</sup>	8493	2	8464	112	98.2 (93.5, 99.8)
HPV 16-related CIN 2/3 or AIS					
Combined Protocols <sup>§</sup>	7402	2	7205	93	97.9 (92.3, 99.8)
HPV 18-related CIN 2/3 or AIS					
Combined Protocols <sup>§</sup>	7382	0	7316	29	100.0 (86.6, 100.0)
HPV 16- or 18-related VIN 2/3					
Study 2	231	0	230	0	Not calculated
Study 3	2219	0	2239	6	100.0 (14.4, 100.0)
Study 4	5322	0	5275	4	100.0 (-50.3, 100.0)
Combined Protocols <sup>§</sup>	7772	0	7744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3					
Study 2	231	0	230	0	Not calculated
Study 3	2219	0	2239	5	100.0 (-10.1, 100.0)
Study 4	5322	0	5275	4	100.0 (-50.3, 100.0)
Combined Protocols <sup>§</sup>	7772	0	7744	9	100.0 (49.5, 100.0)
HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS					
Study 2	235	0	233	3	100.0 (-138.4, 100.0)
Study 3	2241	0	2258	77	100.0 (95.1, 100.0)
Study 4	5388	9	5374	145	93.8 (88.0, 97.2)
Combined Protocols <sup>§</sup>	7864	9	7865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Warts					
Study 2	235	0	233	3	100.0 (-139.5, 100.0)
Study 3	2261	0	2279	58	100.0 (93.5, 100.0)
Study 4	5404	2	5390	132	98.5 (94.5, 99.8)
Combined Protocols <sup>§</sup>	7900	2	7902	193	99.0 (96.2, 99.9)
HPV 6- and 11-related Genital Warts					
Combined Protocols <sup>§</sup>	6932	2	6856	189	99.0 (96.2, 99.9)

\*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (Month 7).

†See Table 14 for analysis of vaccine impact in the general population.

‡Evaluated only the HPV 16 L1 VLP vaccine component of GARDASIL.

§Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.

N = Number of individuals with at least 1 follow-up visit after Month 7

CI = Confidence Interval

Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.

Note 2: The first analysis in the table (i.e., HPV 16- or 18-related CIN 2/3, AIS or worse) was the primary endpoint of the vaccine development plan.

**Note 3: Table 11 does not include cases due to non-vaccine HPV types.**

AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Prophylactic efficacy against overall cervical and genital disease related to HPV 6, 11, 16, and 18 in an extension phase of Study 2, that included data through Month 60, was noted to be 100% (95% CI: 12.3%, 100.0%) among girls and women in the per protocol population naïve to the relevant HPV types.

GARDASIL was efficacious against HPV disease caused by HPV types 6, 11, 16, and 18 in girls and women who were naïve for those specific HPV types at baseline.

#### **14.2 Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in Boys and Men 16 through 26 Years of Age**

The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population. This population consisted of boys and men who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the



relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (Month 7). Efficacy was measured starting after the Month 7 visit.

GARDASIL was efficacious in reducing the incidence of genital warts related to vaccine HPV types 6 and 11 in those boys and men who were PCR negative and seronegative at baseline (Table 12). Efficacy against penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3 or penile/perineal/perianal cancer was not demonstrated as the number of cases was too limited to reach statistical significance.

**Table 12: Analysis of Efficacy of GARDASIL in the PPE\* Population of 16- Through 26-Year-Old Boys and Men for Vaccine HPV Types**

Endpoint	GARDASIL		AAHS Control		% Efficacy (95% CI)
	N†	Number of cases	N	Number of cases	
External Genital Lesions HPV 6-, 11-, 16-, or 18- related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Condyloma	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)

\*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (Month 7).

<sup>†</sup>N = Number of individuals with at least 1 follow-up visit after Month 7

CI = Confidence Interval

AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

### 14.3 Prophylactic Efficacy – Anal Disease Caused by HPV Types 6, 11, 16, and 18 in Boys and Men 16 through 26 Years of Age in the MSM Sub-study

A sub-study of Study 5 evaluated the efficacy of GARDASIL against anal disease (anal intraepithelial neoplasia and anal cancer) in a population of 598 MSM. The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population of Study 5.

GARDASIL was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN) grades 1 (both condyloma and non-acuminate), 2, and 3 related to vaccine HPV types 6, 11, 16, and 18 in those boys and men who were PCR negative and seronegative at baseline (Table 13).

**Table 13: Analysis of Efficacy of GARDASIL for Anal Disease in the PPE\* Population of 16- Through 26-Year-Old Boys and Men in the MSM Sub-study for Vaccine HPV Types**

HPV 6-, 11-, 16-, or 18- related Endpoint	GARDASIL		AAHS Control		% Efficacy (95% CI)
	N <sup>†</sup>	Number of cases	N	Number of cases	
AIN 1/2/3	194	5	208	24	77.5 (39.6, 93.3)
AIN 2/3	194	3	208	13	74.9 (8.8, 95.4)
AIN 1	194	4	208	16	73.0 (16.3, 93.4)
Condyloma Acuminatum	194	0	208	6	100.0 (8.2, 100.0)
Non-acuminate	194	4	208	11	60.4 (-33.5, 90.8)

\*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (month 7).

<sup>†</sup>N = Number of individuals with at least 1 follow-up visit after Month 7

CI = Confidence Interval

AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

### 14.4 Population Impact in Girls and Women 16 through 26 Years of Age

#### *Effectiveness of GARDASIL in Prevention of HPV Types 6-, 11-, 16-, or 18-Related Genital Disease in Girls and Women 16 Through 26 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types*

The clinical trials included girls and women regardless of current or prior exposure to vaccine HPV types, and additional analyses were conducted to evaluate the impact of GARDASIL with respect to HPV 6-, 11-, 16-, and 18-related cervical and genital disease in these girls and women. Here, analyses included events arising among girls and women regardless of baseline PCR status and serostatus, including HPV infections that were present at the start of vaccination as well as events that arose from infections that were acquired after the start of vaccination.

The impact of GARDASIL in girls and women regardless of current or prior exposure to a vaccine HPV type is shown in Table 14. Impact was measured starting 1 month Postdose 1. Prophylactic efficacy denotes the vaccine's efficacy in girls and women who are naïve (PCR negative and seronegative) to the relevant HPV types at Day 1. Vaccine impact in girls and women who were positive for vaccine HPV infection, as well as vaccine impact among girls and women regardless of baseline vaccine HPV PCR status and serostatus are also presented. The majority of CIN and genital warts, VIN, and VaIN related to a vaccine HPV type detected in the group that received GARDASIL occurred as a consequence of HPV infection with the relevant HPV type that was already present at Day 1.

There was no clear evidence of protection from disease caused by HPV types for which girls and women were PCR positive regardless of serostatus at baseline.

**Table 14: Effectiveness of GARDASIL in Prevention of HPV 6, 11, 16, or 18-Related Genital Disease in Girls and Women 16 Through 26 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types**

Endpoint	Analysis	GARDASIL or HPV 16 L1 VLP Vaccine		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
HPV 16- or 18-related CIN 2/3 or AIS	Prophylactic Efficacy*	9346	4	9407	155	97.4 (93.3, 99.3)
	HPV 16 and/or HPV 18 Positive at Day 1 <sup>†</sup>	2870	142	2898	148 <sup>‡</sup>	-- <sup>§</sup>
	Girls and Women Regardless of Current or Prior Exposure to HPV 16 or 18 <sup>¶</sup>	9836	146	9904	303	51.8 (41.1, 60.7)
HPV 16- or 18-related VIN 2/3 or VaIN 2/3	Prophylactic Efficacy*	8642	1	8673	34	97.0 (82.4, 99.9)
	HPV 16 and/or HPV 18 Positive at Day 1 <sup>†</sup>	1880	8	1876	4	-- <sup>§</sup>
	Girls and Women Regardless of Current or Prior Exposure to HPV 16 or 18 <sup>¶</sup>	8955	9	8968	38	76.3 (50.0, 89.9)
HPV 6-, 11-, 16-, 18-related CIN (CIN 1, CIN 2/3) or AIS	Prophylactic Efficacy*	8630	16	8680	309	94.8 (91.5, 97.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1 <sup>†</sup>	2466	186 <sup>#</sup>	2437	213 <sup>#</sup>	-- <sup>§</sup>
	Girls and Women Regardless of Current or Prior Exposure to Vaccine HPV Types <sup>¶</sup>	8819	202	8854	522	61.5 (54.6, 67.4)
HPV 6-, 11-, 16-, or 18-related Genital Warts	Prophylactic Efficacy*	8761	10	8792	252	96.0 (92.6, 98.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1 <sup>†</sup>	2501	51 <sup>‡</sup>	2475	55 <sup>‡</sup>	-- <sup>§</sup>
	Girls and Women Regardless of Current or Prior Exposure to Vaccine HPV Types <sup>¶</sup>	8955	61	8968	307	80.3 (73.9, 85.3)
HPV 6- or 11-related Genital Warts	Prophylactic Efficacy*	7769	9	7792	246	96.4 (93.0, 98.4)
	HPV 6 and/or HPV 11 Positive at Day 1 <sup>†</sup>	1186	51	1176	54	-- <sup>§</sup>
	Girls and Women Regardless of Current or Prior Exposure to Vaccine HPV Types <sup>¶</sup>	8955	60	8968	300	80.1 (73.7, 85.2)

\*Includes all individuals who received at least 1 vaccination and who were HPV-naïve (i.e., seronegative and PCR negative) at Day 1 to the vaccine HPV type being analyzed. Case counting started at 1 month postdose 1.

<sup>†</sup>Includes all individuals who received at least 1 vaccination and who were HPV positive or had unknown HPV status at Day 1, to at least one vaccine HPV type. Case counting started at Day 1.

<sup>‡</sup>Out of the 148 AAHS control cases of 16/18 CIN 2/3, 2 women were missing serology or PCR results for Day 1.

<sup>§</sup>There is no expected efficacy since GARDASIL has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity.

<sup>¶</sup>Includes all individuals who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 month postdose 1.

<sup>#</sup>Includes 2 AAHS control women with missing serology/PCR data at Day 1.

<sup>‡</sup>Includes 1 woman with missing serology/PCR data at Day 1.

CI = Confidence Interval

N = Number of individuals who have at least one follow-up visit after Day 1

Note 1: The 16- and 18-related CIN 2/3 or AIS composite endpoint included data from studies 1, 2, 3, and 4. All other endpoints only included data from studies 2, 3, and 4.

Note 2: Positive status at Day 1 denotes PCR positive and/or seropositive for the respective type at Day 1.

**Note 3: Table 14 does not include disease due to non-vaccine HPV types.**

AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

#### *Effectiveness of GARDASIL in Prevention of Any HPV Type Related Genital Disease in Girls and Women 16 Through 26 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types*

The impact of GARDASIL against the overall burden of dysplastic or papillomatous cervical, vulvar, and vaginal disease regardless of HPV detection, results from a combination of prophylactic efficacy



against vaccine HPV types, disease contribution from vaccine HPV types present at time of vaccination, the disease contribution from HPV types not contained in the vaccine, and disease in which HPV was not detected.

Additional efficacy analyses were conducted in 2 populations: (1) a generally HPV-naïve population (negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1), approximating a population of sexually-naïve girls and women and (2) the general study population of girls and women regardless of baseline HPV status, some of whom had HPV-related disease at Day 1.

Among generally HPV-naïve girls and women and among all girls and women in the study population (including girls and women with HPV infection at Day 1), GARDASIL reduced the overall incidence of CIN 2/3 or AIS; of VIN 2/3 or VaIN 2/3; of CIN (any grade) or AIS; and of Genital Warts (Table 15). These reductions were primarily due to reductions in lesions caused by HPV types 6, 11, 16, and 18 in girls and women naïve (seronegative and PCR negative) for the specific relevant vaccine HPV type. Infected girls and women may already have CIN 2/3 or AIS at Day 1 and some will develop CIN 2/3 or AIS during follow-up, either related to a vaccine or non-vaccine HPV type present at the time of vaccination or related to a non-vaccine HPV type not present at the time of vaccination.

**Table 15: Effectiveness of GARDASIL in Prevention of Any HPV Type Related Genital Disease in Girls and Women 16 Through 26 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types**

Endpoints Caused by Vaccine or Non-vaccine HPV Types	Analysis	GARDASIL		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
CIN 2/3 or AIS	Prophylactic Efficacy*	4616	77	4680	136	42.7 (23.7, 57.3)
	Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	8559	421	8592	516	18.4 (7.0, 28.4)
VIN 2/3 and VaIN 2/3	Prophylactic Efficacy*	4688	7	4735	31	77.1 (47.1, 91.5)
	Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	8688	30	8701	61	50.7 (22.5, 69.3)
CIN (Any Grade) or AIS	Prophylactic Efficacy*	4616	272	4680	390	29.7 (17.7, 40.0)
	Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	8559	967	8592	1189	19.1 (11.9, 25.8)
Genital Warts	Prophylactic Efficacy*	4688	29	4735	169	82.8 (74.3, 88.8)
	Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	8688	132	8701	350	62.5 (54.0, 69.5)

\*Includes all individuals who received at least 1 vaccination and who had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1 and were naïve to 14 common HPV types at Day 1. Case counting started at 1 month postdose 1.

†Includes all individuals who received at least 1 vaccination (regardless of baseline HPV status or Pap test result at Day 1). Case counting started at 1 month postdose 1.

CI = Confidence Interval

AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

#### 14.5 Population Impact in Boys and Men 16 through 26 Years of Age

*Effectiveness of GARDASIL in Prevention of HPV Types 6-, 11-, 16-, or 18-Related Anogenital Disease in Boys and Men 16 Through 26 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types*

Study 5 included boys and men regardless of current or prior exposure to vaccine HPV types, and additional analyses were conducted to evaluate the impact of GARDASIL with respect to HPV 6-, 11-, 16-,

and 18-related anogenital disease in these boys and men. Here, analyses included events arising among boys and men regardless of baseline PCR status and serostatus, including HPV infections that were present at the start of vaccination as well as events that arose from infections that were acquired after the start of vaccination.

The impact of GARDASIL in boys and men regardless of current or prior exposure to a vaccine HPV type is shown in Table 16. Impact was measured starting at Day 1. Prophylactic efficacy denotes the vaccine's efficacy in boys and men who are naïve (PCR negative and seronegative) to the relevant HPV types at Day 1. Vaccine impact in boys and men who were positive for vaccine HPV infection, as well as vaccine impact among boys and men regardless of baseline vaccine HPV PCR status and serostatus are also presented. The majority of anogenital disease related to a vaccine HPV type detected in the group that received GARDASIL occurred as a consequence of HPV infection with the relevant HPV type that was already present at Day 1.

There was no clear evidence of protection from disease caused by HPV types for which boys and men were PCR positive regardless of serostatus at baseline.

**Table 16: Effectiveness of GARDASIL in Prevention of HPV Types 6-, 11-, 16-, or 18-Related Anogenital Disease in Boys and Men 16 Through 26 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types**

Endpoint	Analysis	GARDASIL		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
External Genital Lesions	Prophylactic Efficacy*	1775	13	1770	54	76.3 (56.0, 88.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1 <sup>†</sup>	460	14	453	26	-- <sup>‡</sup>
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types <sup>§</sup>	1943	27	1937	80	66.7 (48.0, 79.3)
Condyloma	Prophylactic Efficacy*	1775	10	1770	49	80.0 (59.9, 90.9)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1 <sup>†</sup>	460	14	453	25	-- <sup>‡</sup>
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types <sup>§</sup>	1943	24	1937	74	68.1 (48.8, 80.7)
PIN 1/2/3	Prophylactic Efficacy*	1775	4	1770	5	20.7 (-268.4, 84.3)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1 <sup>†</sup>	460	2	453	1	-- <sup>‡</sup>
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types <sup>§</sup>	1943	6	1937	6	0.3 (-272.8, 73.4)
AIN 1/2/3	Prophylactic Efficacy*	259	9	261	39	76.9 (51.4, 90.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1 <sup>†</sup>	103	29	116	38	-- <sup>‡</sup>
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types <sup>§</sup>	275	38	276	77	50.3 (25.7, 67.2)
AIN 2/3	Prophylactic Efficacy*	259	7	261	19	62.5 (6.9, 86.7)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1 <sup>†</sup>	103	11	116	20	-- <sup>‡</sup>
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types <sup>§</sup>	275	18	276	39	54.2 (18.0, 75.3)

\*Includes all individuals who received at least 1 vaccination and who were HPV-naïve (i.e., seronegative and PCR negative) at Day 1 to the vaccine HPV type being analyzed. Case counting started at Day 1.

<sup>†</sup>Includes all individuals who received at least 1 vaccination and who were HPV positive or had unknown HPV status at Day 1, to at least one vaccine HPV type. Case counting started at Day 1.

<sup>‡</sup>There is no expected efficacy since GARDASIL has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity.

<sup>§</sup>Includes all individuals who received at least 1 vaccination. Case counting started at Day 1.

CI = Confidence Interval

AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

***Effectiveness of GARDASIL in Prevention of Any HPV Type Related Anogenital Disease in Boys and Men 16 Through 26 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types***

The impact of GARDASIL against the overall burden of dysplastic or papillomatous anogenital disease regardless of HPV detection, results from a combination of prophylactic efficacy against vaccine HPV types, disease contribution from vaccine HPV types present at time of vaccination, the disease contribution from HPV types not contained in the vaccine, and disease in which HPV was not detected.

Additional efficacy analyses from Study 5 were conducted in 2 populations: (1) a generally HPV-naïve population that consisted of boys and men who are seronegative and PCR negative to HPV 6, 11, 16, and 18 and PCR negative to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 at Day 1, approximating a population of sexually-naïve boys and men and (2) the general study population of boys and men regardless of baseline HPV status, some of whom had HPV-related disease at Day 1.

Among generally HPV-naïve boys and men and among all boys and men in Study 5 (including boys and men with HPV infection at Day 1), GARDASIL reduced the overall incidence of anogenital disease (Table 17). These reductions were primarily due to reductions in lesions caused by HPV types 6, 11, 16, and 18 in boys and men naïve (seronegative and PCR negative) for the specific relevant vaccine HPV type. Infected boys and men may already have anogenital disease at Day 1 and some will develop anogenital disease during follow-up, either related to a vaccine or non-vaccine HPV type present at the time of vaccination or related to a non-vaccine HPV type not present at the time of vaccination.

**Table 17: Effectiveness of GARDASIL in Prevention of Any HPV Type Related Anogenital Disease in Boys and Men 16 Through 26 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types**

Endpoint	Analysis	GARDASIL		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
External Genital Lesions	Prophylactic Efficacy*	1275	7	1270	37	81.5 (58.0, 93.0)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types <sup>†</sup>	1943	38	1937	92	59.3 (40.0, 72.9)
Condyloma	Prophylactic Efficacy*	1275	5	1270	33	85.2 (61.8, 95.5)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types <sup>†</sup>	1943	33	1937	85	61.8 (42.3, 75.3)
PIN 1/2/3	Prophylactic Efficacy*	1275	2	1270	4	50.7 (-244.3, 95.5)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types <sup>†</sup>	1943	8	1937	7	-13.9 (-269.0, 63.9)
AIN 1/2/3	Prophylactic Efficacy*	129	12	126	28	54.9 (8.4, 79.1)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types <sup>†</sup>	275	74	276	103	25.7 (-1.1, 45.6)
AIN 2/3	Prophylactic Efficacy*	129	8	126	18	52.5 (-14.8, 82.1)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types <sup>†</sup>	275	44	276	59	24.3 (-13.8, 50.0)

\*Includes all individuals who received at least 1 vaccination and who were seronegative and PCR negative at enrollment to HPV 6, 11, 16 and 18, and PCR negative at enrollment to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. Case counting started at Day 1.

<sup>†</sup>Includes all individuals who received at least 1 vaccination. Case counting started at Day 1.

CI = Confidence Interval

AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

## 14.6 Overall Population Impact

The subject characteristics (e.g. lifetime sex partners, geographic distribution of the subjects) influence the HPV prevalence of the population and therefore the population benefit can vary widely.

The overall efficacy of GARDASIL will vary with the baseline prevalence of HPV infection and disease, the incidence of infections against which GARDASIL has shown protection, and those infections against which GARDASIL has not been shown to protect.

The efficacy of GARDASIL for HPV types not included in the vaccine (i.e., cross-protective efficacy) is a component of the overall impact of the vaccine on rates of disease caused by HPV. Cross-protective efficacy was not demonstrated against disease caused by non-vaccine HPV types in the combined database of the Study 3 and Study 4 trials.

GARDASIL does not protect against genital disease not related to HPV. One woman who received GARDASIL in Study 3 developed an external genital well-differentiated squamous cell carcinoma at Month 24. No HPV DNA was detected in the lesion or in any other samples taken throughout the study.

In 18,150 girls and women enrolled in Study 2, Study 3, and Study 4, GARDASIL reduced definitive cervical therapy procedures by 23.9% (95% CI: 15.2%, 31.7%).

## 14.7 Studies in Women 27 through 45 Years of Age

Study 6 evaluated efficacy in 3253 women 27 through 45 years of age based on a combined endpoint of HPV 6-, 11-, 16- or 18-related persistent infection, genital warts, vulvar and vaginal dysplastic lesions of any grade, CIN of any grade, AIS, and cervical cancer. These women were randomized 1:1 to receive either GARDASIL or AAHS control. The efficacy for the combined endpoint was driven primarily by prevention of persistent infection. There was no statistically significant efficacy demonstrated for CIN 2/3, AIS, or cervical cancer. In post hoc analyses conducted to assess the impact of GARDASIL on the individual components of the combined endpoint, the results in the population of women naïve to the relevant HPV type at baseline were as follows: prevention of HPV 6-, 11-, 16- or 18-related persistent infection (80.5% [95% CI: 68.3, 88.6]), prevention of HPV 6-, 11-, 16- or 18-related CIN (any grade) (85.8% [95% CI: 52.4, 97.3]), and prevention of HPV 6-, 11-, 16- or 18-related genital warts (87.6% [95% CI: 7.3, 99.7]).

Efficacy for disease endpoints was diminished in a population impact assessment of women who were vaccinated regardless of baseline HPV status (full analysis set). In the full analysis set (FAS), efficacy was not demonstrated for the following endpoints: prevention of HPV 16- and 18-related CIN 2/3, AIS, or cervical cancer and prevention of HPV 6- and 11-related condyloma. No efficacy was demonstrated against CIN 2/3, AIS, or cervical cancer in the general population irrespective of HPV type (FAS any type analysis).

## 14.8 Immunogenicity

### *Assays to Measure Immune Response*

The minimum anti-HPV titer that confers protective efficacy has not been determined.

Because there were few disease cases in individuals naïve (PCR negative and seronegative) to vaccine HPV types at baseline in the group that received GARDASIL, it has not been possible to establish minimum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody levels that protect against clinical disease caused by HPV 6, 11, 16, and/or 18.

The immunogenicity of GARDASIL was assessed in 23,951 9- through 45-year-old girls and women (GARDASIL N = 12,634; AAHS control or saline placebo N = 11,317) and 5417 9- through 26-year-old boys and men (GARDASIL N = 3109; AAHS control or saline placebo N = 2308).

Type-specific immunoassays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate.

### *Immune Response to GARDASIL*

The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population. This population consisted of individuals who were seronegative and PCR negative to the relevant HPV type(s) at enrollment, remained HPV PCR negative to the relevant HPV type(s) through 1 month postdose 3 (Month 7), received all 3 vaccinations, and did not deviate from the study protocol in ways that could interfere with the effects of the vaccine.

Immunogenicity was measured by (1) the percentage of individuals who were seropositive for antibodies against the relevant vaccine HPV type, and (2) the Geometric Mean Titer (GMT).

In clinical studies in 16- through 26-year-old girls and women, 99.8%, 99.8%, 99.8%, and 99.4% who received GARDASIL became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month postdose 3 across all age groups tested.

In clinical studies in 27- through 45-year-old women, 98.2%, 97.9%, 98.6%, and 97.1% who received GARDASIL became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month postdose 3 across all age groups tested.

In clinical studies in 16- through 26-year-old boys and men, 98.9%, 99.2%, 98.8%, and 97.4% who received GARDASIL became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month postdose 3 across all age groups tested.

Across all populations, anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs peaked at Month 7 (Table 18 and Table 19). GMTs declined through Month 24 and then stabilized through Month 36 at levels above baseline. Tables 20 and 21 display the persistence of anti-HPV cLIA geometric mean titers by gender and age group. The duration of immunity following a complete schedule of immunization with GARDASIL has not been established.

**Table 18: Summary of Month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI\* Population of Girls and Women**

Population	N <sup>†</sup>	n <sup>‡</sup>	% Seropositive (95% CI)	GMT (95% CI) mMU <sup>§</sup> /mL
<b>Anti-HPV 6</b>				
9- through 15-year-old girls	1122	917	99.9 (99.4, 100.0)	929.2 (874.6, 987.3)
16- through 26-year-old girls and women	9859	3329	99.8 (99.6, 99.9)	545.0 (530.1, 560.4)
27- through 34-year-old women	667	439	98.4 (96.7, 99.4)	435.6 (393.4, 482.4)
35- through 45-year-old women	957	644	98.1 (96.8, 99.0)	397.3 (365.2, 432.2)
<b>Anti-HPV 11</b>				
9- through 15-year-old girls	1122	917	99.9 (99.4, 100.0)	1304.6 (1224.7, 1389.7)
16- through 26-year-old girls and women	9859	3353	99.8 (99.5, 99.9)	748.9 (726.0, 772.6)
27- through 34-year-old women	667	439	98.2 (96.4, 99.2)	577.9 (523.8, 637.5)
35- through 45-year-old women	957	644	97.7 (96.2, 98.7)	512.8 (472.9, 556.1)
<b>Anti-HPV 16</b>				
9- through 15-year-old girls	1122	915	99.9 (99.4, 100.0)	4918.5 (4556.6, 5309.1)
16- through 26-year-old girls and women	9859	3249	99.8 (99.6, 100.0)	2409.2 (2309.0, 2513.8)
27- through 34-year-old women	667	435	99.3 (98.0, 99.9)	2342.5 (2119.1, 2589.6)
35- through 45-year-old women	957	657	98.2 (96.8, 99.1)	2129.5 (1962.7, 2310.5)
<b>Anti-HPV 18</b>				
9- through 15-year-old girls	1122	922	99.8 (99.2, 100.0)	1042.6 (967.6, 1123.3)
16- through 26-year-old girls and women	9859	3566	99.4 (99.1, 99.7)	475.2 (458.8, 492.1)
27- through 34-year-old women	667	501	98.0 (96.4, 99.0)	385.8 (347.6, 428.1)
35- through 45-year-old women	957	722	96.4 (94.8, 97.6)	324.6 (297.6, 354.0)

\*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).

<sup>†</sup>Number of individuals randomized to the respective vaccination group who received at least 1 injection.

<sup>‡</sup>Number of individuals contributing to the analysis.

cLIA = Competitive Luminex Immunoassay

CI = Confidence Interval

GMT = Geometric Mean Titers

<sup>§</sup>mMU = milli-Merck Units

**Table 19: Summary of Month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI\* Population of Boys and Men**

Population	N <sup>†</sup>	n <sup>‡</sup>	% Seropositive (95% CI)	GMT (95% CI) mMU <sup>§</sup> /mL
<b>Anti-HPV 6</b>				
9- through 15-year-old boys	1072	884	99.9 (99.4, 100.0)	1037.5 (963.5, 1117.3)
16- through 26-year-old boys and men	2026	1093	98.9 (98.1, 99.4)	447.8 (418.9, 478.6)
<b>Anti-HPV 11</b>				
9- through 15-year-old boys	1072	885	99.9 (99.4, 100.0)	1386.8 (1298.5, 1481.0)
16- through 26-year-old boys and men	2026	1093	99.2 (98.4, 99.6)	624.3 (588.4, 662.3)
<b>Anti-HPV 16</b>				
9- through 15-year-old boys	1072	882	99.8 (99.2, 100.0)	6056.5 (5601.3, 6548.7)
16- through 26-year-old boys and men	2026	1136	98.8 (97.9, 99.3)	2403.3 (2243.4, 2574.6)
<b>Anti-HPV 18</b>				
9- through 15-year-old boys	1072	887	99.8 (99.2, 100)	1357.4 (1249.4, 1474.7)
16- through 26-year-old boys and men	2026	1175	97.4 (96.3, 98.2)	402.6 (374.6, 432.7)

\*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).

<sup>†</sup>Number of individuals randomized to the respective vaccination group who received at least 1 injection.

<sup>‡</sup>Number of individuals contributing to the analysis.

cLIA = Competitive Luminex Immunoassay

CI = Confidence Interval

GMT = Geometric Mean Titers

<sup>§</sup>mMU = milli-Merck Units



**Table 20: Persistence of Anti-HPV cLIA Geometric Mean Titers in 9- Through 45-Year-Old Girls and Women**

Assay (cLIA)/ Time Point	9- to 15-Year-Old Girls (N* = 1122)		16- to 26-Year-Old Girls and Women (N* = 9859)		27- to 34-Year-Old Women (N* = 667)		35- to 45-Year-Old Women (N* = 957)	
	n <sup>†</sup>	GMT (95% CI) mMU <sup>‡</sup> /mL	n <sup>†</sup>	GMT (95% CI) mMU <sup>‡</sup> /mL	n <sup>†</sup>	GMT (95% CI) mMU <sup>‡</sup> /mL	n <sup>†</sup>	GMT (95% CI) mMU <sup>‡</sup> /mL
<b>Anti-HPV 6</b>								
Month 07	917	929.2 (874.6, 987.3)	3329	545.0 (530.1, 560.4)	439	435.6 (393.4, 482.4)	644	397.3 (365.2, 432.2)
Month 24	214	156.1 (135.6, 179.6)	2788	109.1 (105.2, 113.1)	421	70.7 (63.8, 78.5)	628	69.3 (63.7, 75.4)
Month 36 <sup>§</sup>	356	129.4 (115.6, 144.8)	-	-	399	79.5 (72.0, 87.7)	618	81.1 (75.0, 87.8)
Month 48 <sup>¶</sup>	-	-	2514	73.8 (70.9, 76.8)	391	58.8 (52.9, 65.3)	616	62.0 (57.0, 67.5)
<b>Anti-HPV 11</b>								
Month 07	917	1304.6 (1224.7, 1389.7)	3353	748.9 (726.0, 772.6)	439	577.9 (523.8, 637.5)	644	512.8 (472.9, 556.1)
Month 24	214	218.0 (188.3, 252.4)	2817	137.1 (132.1, 142.3)	421	79.3 (71.5, 87.8)	628	73.4 (67.4, 79.8)
Month 36 <sup>§</sup>	356	148.0 (131.1, 167.1)	-	-	399	81.8 (74.3, 90.1)	618	77.4 (71.6, 83.6)
Month 48 <sup>¶</sup>	-	-	2538	89.4 (85.9, 93.1)	391	67.4 (60.9, 74.7)	616	62.7 (57.8, 68.0)
<b>Anti-HPV 16</b>								
Month 07	915	4918.5 (4556.6, 5309.1)	3249	2409.2 (2309.0, 2513.8)	435	2342.5 (2119.1, 2589.6)	657	2129.5 (1962.7, 2310.5)
Month 24	211	944.2 (804.4, 1108.3)	2721	442.6 (425.0, 460.9)	416	285.9 (254.4, 321.2)	642	271.4 (247.1, 298.1)
Month 36 <sup>§</sup>	353	642.2 (562.8, 732.8)	-	-	399	291.5 (262.5, 323.8)	631	276.7 (254.5, 300.8)
Month 48 <sup>¶</sup>	-	-	2474	326.2 (311.8, 341.3)	394	211.8 (189.5, 236.8)	628	192.8 (176.5, 210.6)
<b>Anti-HPV 18</b>								
Month 07	922	1042.6 (967.6, 1123.3)	3566	475.2 (458.8, 492.1)	501	385.8 (347.6, 428.1)	722	324.6 (297.6, 354.0)
Month 24	214	137.7 (114.8, 165.1)	3002	50.8 (48.2, 53.5)	478	31.8 (28.1, 36.0)	705	26.0 (23.5, 28.8)
Month 36 <sup>§</sup>	357	87.0 (74.8, 101.2)	-	-	453	32.1 (28.5, 36.3)	689	27.0 (24.5, 29.8)
Month 48 <sup>¶</sup>	-	-	2710	33.2 (31.5, 35.0)	444	25.2 (22.3, 28.5)	688	21.2 (19.2, 23.4)

\*N = Number of individuals randomized in the respective group who received at least 1 injection.

<sup>†</sup>n = Number of individuals in the indicated immunogenicity population.<sup>‡</sup>mMU = milli-Merck Units<sup>§</sup>Month 37 for 9- to 15-year-old girls. No serology samples were collected at this time point for 16- to 26-year-old girls and women.<sup>¶</sup>Month 48/End-of-study visits for 16- to 26-year-old girls and women were generally scheduled earlier than Month 48. Mean visit timing was Month 44. The studies in 9- to 15-year-old girls were planned to end prior to 48 months and therefore no serology samples were collected.

cLIA = Competitive Luminex Immunoassay

CI = Confidence Interval

GMT = Geometric Mean Titers



**Table 21: Persistence of Anti-HPV cLIA Geometric Mean Titers in 9- Through 26-Year-Old Boys and Men**

Assay (cLIA)/ Time Point	9- to 15-Year-Old Boys (N* = 1072)		16- to 26-Year-Old Boys and Men (N* = 2026)	
	n <sup>†</sup>	GMT (95% CI) mMU <sup>‡</sup> /mL	n <sup>†</sup>	GMT (95% CI) mMU <sup>‡</sup> /mL
<b>Anti-HPV 6</b>				
Month 07	884	1037.5 (963.5, 1117.3)	1094	447.2 (418.4, 477.9)
Month 24	323	134.1 (119.5, 150.5)	907	80.3 (74.9, 86.0)
Month 36 <sup>§</sup>	342	126.6 (111.9, 143.2)	654	72.4 (68.0, 77.2)
Month 48 <sup>  </sup>	-	-	-	-
<b>Anti-HPV 11</b>				
Month 07	885	1386.8 (1298.5, 1481.0)	1094	624.5 (588.6, 662.5)
Month 24	324	188.5 (168.4, 211.1)	907	94.6 (88.4, 101.2)
Month 36 <sup>§</sup>	342	148.8 (131.1, 169.0)	654	80.3 (75.7, 85.2)
Month 48 <sup>  </sup>	-	-	-	-
<b>Anti-HPV 16</b>				
Month 07	882	6056.5 (5601.4, 6548.6)	1137	2401.5 (2241.8, 2572.6)
Month 24	322	938.2 (825.0, 1067.0)	938	347.7 (322.5, 374.9)
Month 36 <sup>§</sup>	341	708.8 (613.9, 818.3)	672	306.7 (287.5, 327.1)
Month 48 <sup>  </sup>	-	-	-	-
<b>Anti-HPV 18</b>				
Month 07	887	1357.4 (1249.4, 1474.7)	1176	402.6 (374.6, 432.6)
Month 24	324	131.9 (112.1, 155.3)	967	38.7 (35.2, 42.5)
Month 36 <sup>§</sup>	343	113.0 (94.7, 135.0)	690	33.4 (30.9, 36.1)
Month 48 <sup>  </sup>	-	-	-	-

\*N = Number of individuals randomized in the respective group who received at least 1 injection.

<sup>†</sup>n = Number of individuals in the indicated immunogenicity population.

<sup>‡</sup>mMU = milli-Merck Units

<sup>§</sup>Month 36 time point for 16- to 26-year-old boys and men; Month 37 for 9- to 15-year-old boys.

<sup>||</sup>The studies in 9- to 15-year-old boys and girls and 16- to 26-year-old boys and men were planned to end prior to 48 months and therefore no serology samples were collected.

cLIA = Competitive Luminex Immunoassay

CI = Confidence Interval

GMT = Geometric Mean Titers

Tables 18 and 19 display the Month 7 immunogenicity data for girls and women and boys and men. Anti-HPV responses 1 month postdose 3 among 9- through 15-year-old adolescent girls were non-inferior to anti-HPV responses in 16- through 26-year-old girls and women in the combined database of immunogenicity studies for GARDASIL. Anti-HPV responses 1 month postdose 3 among 9- through 15-year-old adolescent boys were non-inferior to anti-HPV responses in 16- through 26-year-old boys and men in Study 5.

On the basis of this immunogenicity bridging, the efficacy of GARDASIL in 9- through 15-year-old adolescent girls and boys is inferred.

#### *GMT Response to Variation in Dosing Regimen in 18- Through 26-Year-Old Women*

Girls and women evaluated in the PPE population of clinical studies received all 3 vaccinations within 1 year of enrollment. An analysis of immune response data suggests that flexibility of  $\pm 1$  month for Dose 2 (i.e., Month 1 to Month 3 in the vaccination regimen) and flexibility of  $\pm 2$  months for Dose 3 (i.e., Month 4 to Month 8 in the vaccination regimen) do not impact the immune responses to GARDASIL.

*Duration of the Immune Response to GARDASIL*

The duration of immunity following a complete schedule of immunization with GARDASIL has not been established. The peak anti-HPV GMTs for HPV types 6, 11, 16, and 18 occurred at Month 7. Anti-HPV GMTs for HPV types 6, 11, 16, and 18 were similar between measurements at Month 24 and Month 60 in Study 2.

**14.9 Long-Term Follow-Up Studies**

The protection of GARDASIL against HPV-related disease continues to be studied over time in populations including adolescents (boys and girls) and women who were enrolled in the Phase 3 studies.

*Persistence of Effectiveness*

An extension of Study 4 used national healthcare registries in Denmark, Iceland, Norway, and Sweden to monitor endpoint cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, or vaginal cancer among 2,650 girls and women 16 through 23 years of age at enrollment who were randomized to vaccination with GARDASIL and consented to be followed in the extension study. An interim analysis of the per-protocol effectiveness population included 1,902 subjects who completed the GARDASIL vaccination series within one year, were naïve to the relevant HPV type through 1 month postdose 3, had no protocol violations, and had follow-up data available. The median follow-up from initial vaccination was 6.7 years with a range of 2.8 to 8.4 years. No cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, or vaginal cancer were observed over a total of 5,765 person-years at risk.

An extension of a Phase 3 study (Study 7) in which 614 girls and 565 boys 9 through 15 years of age at enrollment were randomized to vaccination with GARDASIL actively followed subjects for endpoint cases of HPV 6-, 11-, 16-, or 18-related persistent infection, CIN (any grade), AIS, VIN, VaIN, cervical cancer, vulvar cancer, vaginal cancer, and genital lesions from the initiation of sexual activity or age 16 onwards. An interim analysis of the per-protocol effectiveness population included 246 girls and 168 boys who completed the GARDASIL vaccination series within one year, were seronegative to the relevant HPV type at initiation of the vaccination series, and had not initiated sexual activity prior to receiving the third dose of GARDASIL. The median follow-up, from the first dose of vaccine, was 7.2 years with a range of 0.5 to 8.5 years. No cases of persistent infection of at least 12 months' duration and no cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, VIN, VaIN, cervical cancer, vulvar cancer, vaginal cancer, or genital lesions were observed over a total 1,105 person-years at risk. There were 4 cases of HPV 6-, 11-, 16-, or 18-related persistent infection of at least 6 months' duration, including 3 cases related to HPV 16 and 1 case related to HPV 6, none of which persisted to 12 months' duration.

*Persistence of the Immune Response*

The interim reports of the two extension studies described above included analyses of type-specific anti-HPV antibody titers at 9 years postdose 1 for girls and women 16 through 23 years of age at enrollment (range of 1,178 to 1,331 subjects with evaluable data across HPV types) and at 8 years postdose 1 for boys and girls 9 through 15 years of age at enrollment (range of 436 to 440 subjects with evaluable data across HPV types). Anti-HPV 6, 11, 16, and 18 GMTs as measured by cLIA were decreased compared with corresponding values at earlier time points, but the proportions of seropositive subjects ranged from 88.4% to 94.4% for anti-HPV 6, from 89.1% to 95.5% for anti-HPV 11, from 96.8% to 99.1% for anti-HPV 16, and from 60.0% to 64.1% for anti-HPV 18.

**14.10 Studies with RECOMBIVAX HB [hepatitis B vaccine (recombinant)]**

The safety and immunogenicity of co-administration of GARDASIL with RECOMBIVAX HB [hepatitis B vaccine (recombinant)] (same visit, injections at separate sites) were evaluated in a randomized, double-blind, study of 1871 women aged 16 through 24 years at enrollment. The race distribution of the girls and women in the clinical trial was as follows: 61.6% White; 1.6% Hispanic (Black and White); 23.8% Other; 11.9% Black; 0.8% Asian; and 0.3% American Indian.

Subjects either received GARDASIL and RECOMBIVAX HB (n = 466), GARDASIL and RECOMBIVAX HB-matched placebo (n = 468), RECOMBIVAX HB and GARDASIL-matched placebo (n = 467) or RECOMBIVAX-matched placebo and GARDASIL-matched placebo (n = 470) at Day 1, Month 2 and Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series.

Concomitant administration of GARDASIL with RECOMBIVAX HB [hepatitis B vaccine (recombinant)] did not interfere with the antibody response to any of the vaccine antigens when GARDASIL was given concomitantly with RECOMBIVAX HB or separately.

#### **14.11 Studies with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)]**

The safety and immunogenicity of co-administration of GARDASIL with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] (same visit, injections at separate sites) were evaluated in an open-labeled, randomized, controlled study of 1040 boys and girls 11 through 17 years of age at enrollment. The race distribution of the subjects in the clinical trial was as follows: 77.7% White; 6.8% Hispanic (Black and White); 1.4% Multi-racial; 12.3% Black; 1.2% Asian; 0.2% Indian; and 0.4% American Indian.

One group received GARDASIL in one limb and both Menactra and Adacel, as separate injections, in the opposite limb concomitantly on Day 1 (n = 517). The second group received the first dose of GARDASIL on Day 1 in one limb then Menactra and Adacel, as separate injections, at Month 1 in the opposite limb (n = 523). Subjects in both vaccination groups received the second dose of GARDASIL at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series (1 dose for Menactra and Adacel and 3 doses for GARDASIL).

Concomitant administration of GARDASIL with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] did not interfere with the antibody response to any of the vaccine antigens when GARDASIL was given concomitantly with Menactra and Adacel or separately.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

All presentations for GARDASIL contain a suspension of 120 mcg L1 protein from HPV types 6, 11, 16, and 18 in a 0.5-mL dose. GARDASIL is supplied in vials and syringes.

Carton of one 0.5-mL single-dose vial. **NDC 0006-4045-00.**

Carton of ten 0.5-mL single-dose vials. **NDC 0006-4045-41.**

Carton of six 0.5-mL single-dose prefilled Luer-Lok<sup>®</sup> syringes with tip caps. **NDC 0006-4109-09.**

Carton of ten 0.5-mL single-dose prefilled Luer-Lok<sup>®</sup> syringes with tip caps. **NDC 0006-4109-02.**

Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light.

GARDASIL should be administered as soon as possible after being removed from refrigeration.

GARDASIL can be out of refrigeration (at temperatures at or below 25°C/77°F), for a total time of not more than 72 hours.

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform the patient, parent, or guardian:

- Vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL should continue to undergo cervical cancer screening per standard of care.
- Recipients of GARDASIL should not discontinue anal cancer screening if it has been recommended by a health care provider.
- GARDASIL has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity.
- Since syncope has been reported following vaccination sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended.
- Vaccine information is required to be given with each vaccination to the patient, parent, or guardian.
- Information regarding benefits and risks associated with vaccination.

- GARDASIL is not recommended for use in pregnant women.
  - Importance of completing the immunization series unless contraindicated.
  - Report any adverse reactions to their health care provider.
- 

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# **EXHIBIT 258**

# Safety and Persistent Immunogenicity of a Quadrivalent Human Papillomavirus Types 6, 11, 16, 18 L1 Virus-Like Particle Vaccine in Preadolescents and Adolescents

## A Randomized Controlled Trial

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**Objective:** Administration of a quadrivalent HPV-6/11/16/18 vaccine to 16- to 26-year-old women was highly effective in preventing HPV-6/11/16/18-related cervical/vulvar/vaginal precancerous lesions and genital warts. As the risk of acquiring HPV significantly rises after sexual debut, HPV vaccines should have the greatest benefit in sexually naive adolescents. We evaluated the tolerability and immunogenicity of quadrivalent vaccine in males and females 9 to 15 years of age through 18 months postenrollment.

**Methods:** In this randomized, double-blind trial, 1781 sexually naive children were assigned (2:1) to quadrivalent HPV-6/11/16/18 vaccine or saline placebo administered at day 1 and months 2 and 6. Serum neutralizing anti-HPV-6/11/16/18 responses were summarized as geometric mean titers (GMTs) and seroconversion rates. Primary analyses were done per-protocol (subjects received 3 doses, had no major protocol violations and were HPV type-specific seronegative at day 1). Adverse experiences were collected by diary card.

**Results:** At month 7, seroconversion rates were  $\geq 99.5\%$  for the 4 vaccine-HPV-types. GMTs and seroconversion rates in boys were noninferior to those in girls ( $P < 0.001$ ). At month 18,  $\geq 91.5\%$  of vaccine recipients were seropositive, regardless of gender. A higher proportion of vaccine recipients (75.3%) than placebo recipients (50.0%) reported one or more injection-site adverse experiences following any vaccination. Rates of fever were similar between vaccination groups. No serious vaccine-related adverse experiences were reported.

**Conclusions:** In 9- to 15-year-old adolescents, the quadrivalent vaccine was generally well tolerated and induced persistent anti-HPV serologic responses in the majority of subjects for at least 12

months following completion of a three-dose regimen. The vaccine durability supports universal HPV vaccination programs in adolescents to reduce the burden of clinical HPV disease, particularly cervical cancer and precancers.

**Key Words:** HPV, vaccine, immunogenicity, reactogenicity, pediatric, noninferiority

(*Pediatr Infect Dis J* 2007;26: 201–209)

Human papillomavirus (HPV) infection causes cervical cancer and genital warts.<sup>1–6</sup> HPV infection is common, with a lifetime risk exceeding 50% for sexually active males and females.<sup>7</sup> Studies have shown that the 5 years following sexual debut represent the period of highest risk for acquisition of HPV infection.<sup>8–10</sup> In most countries, the median/mean age of sexual debut is between 15 and 16 years of age.<sup>11,12</sup> Because HPV is the major cause of cervical cancer, the high prevalence of genital HPV infection is considered a serious worldwide health issue.<sup>7</sup>

The genital HPV family is composed of  $\sim 35$  distinct types. These HPV types are divided into high risk (associated with the development of anogenital cancers) and low risk (associated with the development of dysplasia and anogenital warts, but rarely cancer). Four HPV types have been associated with the majority of HPV-related clinical disease. HPV types 16 and 18 cause approximately 70% of cervical cancers, HPV-6 and HPV-11 cause approximately 90% of genital warts (men and women) and types HPV-6/11/16/18 together cause a significant proportion of cervical intraepithelial neoplasia (CIN) leading to abnormal Papanicolaou (Pap) smears.<sup>2,5,14–16</sup>

The well-established link between HPV and anogenital cancers, high- and low-grade dysplasia, and genital warts, has led to the development of prophylactic (ie, prior to infection) HPV vaccines. Recent studies in young adult women have shown that prophylactic administration of virus-like particle (VLP) vaccines based on the HPV L1 capsid protein are highly efficacious and immunogenic.<sup>17–22</sup> A phase II, randomized, placebo-controlled study of a quadrivalent HPV-6/

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11/16/18 L1 VLP vaccine included 551 women.<sup>20–22</sup> Through 5.0 years, the overall vaccine efficacy was 96% for preventing HPV 6-, 11-, 16- or 18-related persistent infection and 100% for preventing HPV 6-, 11-, 16- or 18-related disease. In phase III studies conducted in >18,000 young adult women, prophylactic administration of this quadrivalent HPV vaccine was 100% effective in preventing HPV-6, HPV-11, HPV-16 or HPV-18-related precancerous or cancerous lesions of the cervix, vagina and vulva, as well as genital warts through approximately 2 years postvaccination.<sup>18,19</sup> In young adult women, a three-dose regimen of quadrivalent HPV vaccine resulted in robust anti-HPV type-specific immunogenic responses.<sup>20,22</sup> Vaccine-induced antibody responses 1 month following completion of the vaccination series were substantially higher than those observed following natural infection<sup>22</sup>; and in a subset of women with extended follow-up, these responses have been shown to persist (ie, geometric mean titers remained above the seropositivity threshold) through at least 5 years.<sup>21</sup>

If proven safe and effective, a vaccine that prevents cervical cancer, other cervical lesions and genital warts due to HPV-6/11/16/18 will represent a major public health advance. Because the highest risk of acquiring HPV infection is within the 5 years after sexual debut, prophylactic vaccination against HPV should have the greatest benefit in sexually naive adolescents.<sup>23–25</sup> A previous study in male and female adolescents 10 to 15 years of age showed that administration of quadrivalent HPV vaccine is generally well tolerated and produces up to 2-fold higher anti-HPV responses in adolescents compared with young adult women.<sup>26</sup> However, the study was limited by the absence of long-term vaccination follow-up in the adolescent cohort. The present study was designed to assess vaccine safety, to compare the immunogenicity of quadrivalent vaccine in young male versus female adolescents and to explore the safety and duration of immunity of this vaccine for 12 months after the primary series. Unique to this study, the safety comparator for the quadrivalent HPV vaccine was a non-aluminum-containing placebo, whereas all other studies to date have compared the vaccine with aluminum-containing placebo.

## METHODS

### Study Population

Between October 2003 and March 2004, 1781 healthy, sexually naive boys and girls 9 to 15 years of age were enrolled at 47 study sites located in 10 countries in North America, Latin America, Europe and Asia. Inclusion/exclusion criteria were similar to that described for a noninferiority immunogenicity bridging study.<sup>26</sup> An Institutional Review Board for each clinical site approved the study protocol. At enrollment, written consent was obtained from each participant and his/her legal guardian.

### Study Vaccine

The quadrivalent HPV-6/11/16/18 L1 VLP vaccine (GARDASIL/SILGARD, Merck and Co., Inc., Whitehouse Station, NJ) has been described.<sup>22</sup> The placebo used in this study contained identical components to those in the vaccine,

with the exception of HPV L1 VLPs and aluminum adjuvant, in a total carrier volume of 0.5 mL. Vaccine and placebo were visually distinguishable.

### Study Design

The trial (Merck protocol V501-018) was a randomized, double-blind (with sponsor blinding), placebo-controlled, multicenter study. Enrollment was stratified by age (2:1 ratio of 9- to 12-year-old subjects and 13- to 15-year-old subjects) and by gender (1:1). Randomization schedules were computer-generated using a blocking factor of 6. An interactive voice response system was used to allocate study subjects and to assign allocation numbers. Subjects were randomized in a 2:1 ratio within study centers to receive 3 intramuscular injections of either quadrivalent HPV vaccine or non-aluminum-containing placebo at day 1, month 2 and month 6. The deltoid muscle was the preferred site for intramuscular injection. Vaccine/placebo was administered using a 1.0-mL syringe with needle length of 1 to 2 inches (22–23 gauge).

As the vaccine and placebo used in this study were visually distinguishable, they were prepared and administered by unblinded study personnel not otherwise involved in the care and management of the study participants. The success of blinding was assessed by designated unblinded sponsor and study personnel. To ensure effective monitoring of adverse experiences, an independent safety monitor (not employed by the sponsor) was used. Otherwise, the subject and the investigator, study site personnel, and laboratory personnel conducting the clinical assays were blinded to vaccination group throughout the study. The sponsor's clinical, statistical and data management teams were blinded until the primary analysis at month 7.

A medical history and physical examination were conducted at day 1. If the participant was found to have a temperature of  $\geq 100^{\circ}\text{F}$  (oral) within 24 hours before an injection, the injection was postponed. For all female subjects, a pregnancy test (sensitive to 25 IU human chorionic gonadotropin) was performed prior to each injection.

Blood samples were obtained on day 1 prior to the first vaccination, month 7 and month 18. Serum specific neutralizing antibodies to HPV-6/11/16/18 were measured using a competitive Luminex immunoassay (cLIA), as described.<sup>27</sup> Seropositivity was defined as anti-HPV serum cLIA levels  $\geq 20$ , 16, 20 and 24 mMU/mL for HPV-6, HPV-11, HPV-16 and HPV-18, respectively.<sup>27</sup> Seropositivity information was not available prior to the day 1 vaccination. However, if a subject was found to have anti-HPV levels above any serostatus cutoffs at day 1 (prevaccination), indicating prior exposure to one or more vaccine HPV-types, this result was communicated to the primary investigator who had enrolled the subject. After unblinding of the data, investigators were to communicate the finding to the subject and to the parent/legal guardian with appropriate counseling.

### Adverse Event Monitoring

Participants were observed for at least 30 minutes after each vaccination for any immediate reaction. Temperatures were recorded orally for 5 days following each injection. All adverse experiences were collected daily by the parent/legal



guardian on a vaccination report card for 14 days following each vaccination. Follow-up at months 2, 6, 7, 12 and 18 included an interview to assess general safety. In addition, at any time during the study, all deaths (regardless of cause) and serious adverse experiences that were considered by the investigator to be vaccine-related were to be reported. The relationship between adverse experiences and vaccine was reported by the investigator according to his/her best clinical judgment, based on exposure, time course, likely cause and probability with vaccine profile.

## Statistical Analyses

**Safety.** The primary safety hypothesis stated that a 3-dose regimen of quadrivalent HPV vaccine is generally well tolerated in adolescents and preadolescents. A detailed tolerability analysis was performed with emphasis on the following prespecified adverse experiences: vaccine-related adverse experiences, injection-site adverse experiences (swelling/redness and pain/tenderness/soreness), systemic adverse experiences (muscle/joint pain, headaches, hives, rashes and diarrhea), severe adverse experiences, and fever. All subjects who received at least one injection and had follow-up data were included in the safety summaries. Adverse experiences were summarized descriptively as frequencies and percentages by vaccination group and type of adverse experience, by vaccination visit and across all vaccination visits. Elevated temperatures ( $\geq 100^{\circ}\text{F}$  oral or oral equivalent) within 5 days following each vaccination were summarized in a similar manner. In addition, risk differences and associated 95% confidence intervals (CI) were computed comparing the vaccine and placebo groups across all vaccination visits with respect to adverse experiences with  $\geq 1\%$  incidence in either vaccination group. *P* values were computed only for those adverse experiences that were prompted for on the vaccination report card (elevated temperatures, injection-site pain, injection-site swelling, injection-site redness, muscle/joint pain, headaches, hives, rashes and diarrhea). Adverse experiences were also summarized separately for boys and girls (within each vaccination group) and by age group. No formal comparisons were made between boys and girls or age groups with respect to adverse experiences.

## Immunogenicity

The secondary hypothesis of this study stated that the immune responses to quadrivalent HPV vaccine in preadolescent and adolescent boys are noninferior to the responses in preadolescent and adolescent girls, as measured by anti-HPV GMTs and seroconversion rates one month postdose 3 (month 7). Analyses of noninferiority were conducted based on HPV type-specific per-protocol populations. The per-protocol populations for HPV-6, HPV-11, HPV-16 and HPV-18 consisted of subjects who were seronegative to the relevant HPV type(s) at enrollment, received all 3 doses of vaccine or placebo within the protocol-specified time frames and did not violate the protocol.

The evaluation of noninferiority of boys to girls with respect to the percentage of subjects who seroconverted for each HPV type by month 7 used 4 one-sided tests of noninferiority (one corresponding to each HPV type) conducted at

the 0.025 level, based on the methods of Miettinen and Nurminen.<sup>28</sup> To reject the null hypothesis for a given HPV type, the lower bound of the 95% CI on the difference in the percentages of seroconverters (boys minus girls) for that type had to be greater than  $-5$  percentage points.

Noninferiority of boys to girls with respect to month 7 anti-HPV GMTs was tested using an analysis of variance (ANOVA) model. The natural log of the individual titers of the subjects in the quadrivalent HPV vaccine group was modeled as a function of gender, age at enrollment and geographic region, which were considered fixed effects. The analysis was performed using the mean squared error from the ANOVA model as an estimate of variance and a one-sided test for the similarity of 2 means was performed at the 0.025 level. The antilog of the estimated treatment difference in the ANOVA model, and the associated 95% CI, was computed. To reject the null hypothesis for a given HPV type, the lower bound of the 95% CI on the ratio of month 7 GMTs (boys/girls) for that type had to be greater than 0.5.

To declare the immune responses in boys noninferior to those in girls, the statistical criterion had to be met for each HPV type and for each endpoint (month 7 GMTs and seroconversion rates).

A secondary immunogenicity objective was to describe the persistence of immune response to the quadrivalent HPV vaccine. To address this objective, GMTs for each vaccine HPV type, with associated 95% CIs, were summarized at month 18, 1 year following completion of the primary vaccination regimen. In addition, percentages of per-protocol subjects who remained seropositive at month 18 were calculated.

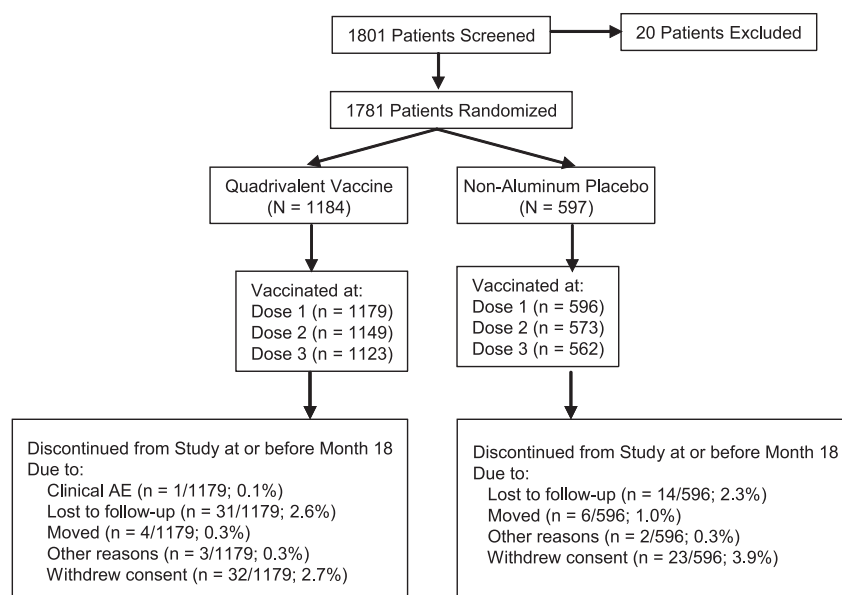
## Determination of Sample Size and Power Analysis to Address Study Hypotheses

The primary hypothesis in this study relates to the tolerability of the quadrivalent HPV vaccine. If no vaccine-related serious adverse experiences were observed among 1100 vaccinated subjects, this study provided 95% confidence (one-sided) that the true incidence was no greater than 0.27%. With at least 847, 847, 836 and 836 evaluable subjects in the per-protocol populations related to HPV-6, HPV-11, HPV-16 and HPV-18, respectively (based on predicted rates of attrition and baseline seropositivity rates), the study had  $>99\%$  power to rule out a  $\geq 2$ -fold difference in the ratio of GMTs ( $\alpha = 0.025$ , 1-sided) for each vaccine HPV type and  $>99\%$  power to rule out a  $\geq 5$ -percentage-point difference in seroconversion rates between the 2 groups ( $\alpha = 0.025$ , 1-sided) for each HPV type. If the 2 immunogenicity hypotheses were independent, the overall power of the study to declare noninferiority of immune responses in boys relative to girls was  $>99\%$ .

The analyses presented here include all safety and immunogenicity data from visits that occurred on or before November 7, 2005. At this time point, the duration of participation was approximately 1.5 years.

## Role of the Funding Source

The studies were designed by the sponsor (Merck and Co., Inc.) in collaboration with clinical site investigators. The sponsor collected the data, monitored the conduct of the



**FIGURE 1.** Subject disposition flowchart.

study, performed the statistical analysis and coordinated the writing of the manuscript with all authors. Data were unblinded for statistical analyses after the databases were locked. The authors were actively involved in data analysis and interpretation and approved the final manuscript. All authors vouch for the veracity and completeness of the data and the data analyses.

## RESULTS

**Study Population.** Of 1801 subjects screened for eligibility, 1781 were enrolled and randomized to receive quadrivalent vaccine or placebo (Fig. 1). Twenty subjects were screened but not randomized. Of these, 11 withdrew consent prior to randomization, 5 did not meet the inclusion/exclusion criteria, one was unable to provide a sample for the required urine pregnancy test, one was not randomized due to unavailability of the protocol-specified needles, and 2 did not meet the

enrollment cutoff for their gender/age group. Of the randomized subjects, 1775 (>99%) received at least one injection. Six subjects withdrew consent and were not vaccinated. A summary of the number of subjects who discontinued from the study, by vaccination group, is provided in Figure 1. The proportions of subjects who failed to complete the vaccination regimen, and the distributions of reasons for discontinuation, were generally similar between the 2 vaccination groups. Lost to follow-up (45 of 1775) and withdrawal of consent (55 of 1775) were the most common reasons for discontinuation.

Key demographic characteristics were generally similar between boys and girls and between subjects who received quadrivalent HPV vaccine or placebo (Table 1). Among all randomized participants, the median age was 12 years and the mean ( $\pm$ standard deviation) body mass index (BMI) was 20.5 ( $\pm$ 4.6). The majority of randomized subjects (60.9%)

**TABLE 1.** Summary of Subject Characteristics by Gender and by Vaccination Group at Enrollment

	Quadrivalent HPV (types 6, 11, 16, 18) L1 VLP Vaccine		Non-Aluminum Placebo		Total (N = 1781)
	Boys (N = 567)	Girls (N = 617)	Boys (N = 275)	Girls (N = 322)	
Age (yr)					
Mean $\pm$ SD	12.0 $\pm$ 1.9	11.9 $\pm$ 1.9	11.8 $\pm$ 1.8	11.8 $\pm$ 1.9	11.9 $\pm$ 1.9
Range	9–16	9–15	9–15	9–15	9–16
Body mass index [weight (kg)/height (m) <sup>2</sup> ]					
Mean $\pm$ SD	20.2 $\pm$ 4.4	20.5 $\pm$ 4.5	20.3 $\pm$ 4.3	21.1 $\pm$ 5.1	20.5 $\pm$ 4.6
Range	12–41	9–46	14–39	13–51	9–51
Race/ethnicity [no. (%)]					
White	346 (61.0)	370 (60.0)	162 (58.9)	207 (64.3)	1085 (60.9)
Hispanic American	123 (21.7)	137 (22.2)	61 (22.2)	69 (21.4)	390 (21.9)
Asian	67 (11.8)	82 (13.3)	37 (13.5)	33 (10.2)	219 (12.3)
Black	26 (4.6)	24 (3.9)	11 (4.0)	10 (3.1)	71 (4.0)
Native American/Other	5 (0.9)	4 (0.6)	4 (1.5)	3 (0.9)	16 (0.9)
Seropositive to HPV 6, 11, 16, or 18* [no. (%)]	9/555 (1.6)	11/602 (1.8)	4/269 (1.5)	14/314 (4.5)	38/1740 (2.2)

\*Numerator = number of subjects who were seropositive at day 1 to one or more of HPV types 6, 11, 16 or 18; denominator = number of subjects with day 1 serum sample.

**TABLE 2.** Summary of Exclusions From Per-Protocol Immunogenicity Population by Gender

	Quadrivalent HPV (types 6, 11, 16, 18) L1 VLP Vaccine		
	Boys	Girls	Total
No. of subjects included in per-protocol population related to:			
HPV 6	456	492	948
HPV 11	457	492	949
HPV 16	455	489	944
HPV 18	458	494	952
Reasons for exclusion from per-protocol populations*			
General protocol violation	57	72	129
Missing or invalid day 1 serology sample/results			
HPV 6	10	14	24
HPV 11	10	14	24
HPV 16	10	15	25
HPV 18	9	14	23
Missing or invalid month 7 serology sample/results			
HPV 6	24	19	43
HPV 11	23	19	42
HPV 16	25	22	47
HPV 18	26	19	45
Month 7 serology sample out of acceptable day range	28	30	58
Day 1 seropositive to HPV 6 or 11 <sup>†</sup>	4	5	9
Day 1 seropositive to HPV 16 <sup>†</sup>	4	4	8
Day 1 seropositive to HPV 18 <sup>†</sup>	1	2	3

\*A subject may appear in more than one category; however, a subject is counted only once in the total number excluded.

<sup>†</sup>Exclusion due to day 1 seropositivity applies only to respective per-protocol population.

were white, followed by Hispanic American (21.9%). Day 1 anti-HPV titers above the seropositivity cutoff for a given HPV type (indicative of previous exposure to that type) were detected in 38 of 1740 (2.2%) of subjects. Sixteen subjects were positive to HPV-6, 2 were positive to HPV-11, 18 were positive to HPV-16 and 5 were positive to HPV-18. Among these baseline seropositive subjects, 66% were girls and 34% were boys.

**Immunogenicity.** The immune response generated by a 3-dose regimen of quadrivalent HPV vaccine was compared between boys and girls. Analyses of noninferiority were conducted in the HPV-6, HPV-11, HPV-16 and HPV-18 per-protocol cohorts, which included 948, 949, 944, and 952 quadrivalent vaccine recipients, respectively (Table 2). Approximately 80% of the study participants

met the protocol's criteria for inclusion in the per-protocol evaluation (Table 2). The most common reason for exclusion was a general protocol violation (129 subjects), such as an incomplete vaccination series or vaccination outside of an acceptable day range. The proportion of girls excluded from the per-protocol analysis of each vaccine HPV type was slightly higher (19.6–20.4%) than the proportion of boys excluded (18.7–19.2%).

For each of the 4 vaccine types, ≥99.5% of subjects in the respective per-protocol immunogenicity cohort had seroconverted by 1 month after completion of the 3-dose regimen, regardless of gender (Table 3). The lower bound of the 95% CI for the difference (boys minus girls) in seroconversion rates was ≤−5% points for each vaccine type ( $P < 0.001$  for each vaccine component).

**TABLE 3.** Per-Protocol Analyses of Month 7 Anti-HPV Responses

Parameter	Boys		Girls		Difference/Fold Difference (95% CI)*
	n	Response	n	Response	
Anti-HPV 6					
% Seroconversion	456	99.8	492	99.8	0.0 (−1.0, 1.0)
GMT (mMU/mL)		1007		808	1.3 (1.0, 1.5)
Anti-HPV 11					
% Seroconversion	457	99.8	492	99.8	0.0 (−1.0, 1.0)
GMT (mMU/mL)		1334		1187	1.1 (0.9, 1.4)
Anti-HPV 16					
% Seroconversion	455	99.5	489	99.8	−0.2 (−1.4, 0.8)
GMT (mMU/mL)		6316		4490	1.4 (1.1, 1.8)
Anti-HPV 18					
% Seroconversion	458	99.8	494	99.6	0.2 (−0.8, 1.3)
GMT (mMU/mL)		1581		1071	1.5 (1.2, 1.9)

\*Difference = Boys minus girls; Fold difference = boys divided by girls.  $P < 0.001$  for all tests of noninferiority of immune responses in boys to those in girls (for all 4 vaccine HPV types for both endpoints).

**TABLE 4.** Per-Protocol Summary of Month 18 Anti-HPV Responses

Parameter	Boys			Girls		
	n	Response	95% CI	n	Response	95% CI
Anti-HPV 6						
% Seroconversion	449	97.8	(95.9, 98.9)	481	97.9	(96.2, 99.0)
GMT (mMU/mL)		227	(204, 251)		213	(195, 232)
Anti-HPV 11						
% Seroconversion	450	99.3	(98.1, 99.9)	481	99.2	(97.9, 99.8)
GMT (mMU/mL)		292	(263, 323)		300	(273, 330)
Anti-HPV 16						
% Seroconversion	448	99.3	(98.1, 99.9)	478	99.8	(98.8, 100)
GMT (mMU/mL)		1,402	(1252, 1570)		1,250	(1134, 1378)
Anti-HPV 18						
% Seroconversion	451	92.5	(89.6, 94.7)	483	91.5	(88.7, 93.8)
GMT (mMU/mL)		233	(201, 270)		181	(159, 205)

Table 3 displays the results of the analysis of noninferiority with respect to GMTs as measured 1-month post-completion of the vaccination regimen. The table displays the GMTs, along with the fold differences in GMTs (boys divided by girls), and the 95% CIs on the fold differences. The lower bound of the 95% CI on the fold difference exceeded 0.5 for each vaccine HPV type, thus supporting the conclusion that the anti-HPV GMTs in boys are noninferior to those in girls ( $P < 0.001$  for each vaccine component). Of note, for all vaccine types, numerically higher GMTs were observed in boys compared with girls.

Baseline characteristics were evaluated for their potential to affect anti-HPV responses. The magnitude of vaccine-induced anti-HPV responses varied with age at first vaccination. At 1-month postdose 3, anti-HPV-6, anti-HPV-11, anti-HPV-16 and anti-HPV-18 GMTs were approximately 1.4-, 1.5-, 1.5- and 1.6-fold higher, respectively, in subjects who were 9 to 12 years old compared with subjects who were 13 to 15 years old at first vaccination. A number of vaccines have been shown to produce suboptimal immune responses if administered subcutaneously, and for the very overweight, many IM injections end up subcutaneous. In general, anti-HPV responses for HPV types 6 and 11 did not appear to be affected by BMI. Subjects with BMIs less than 28 had generally comparable GMTs to subjects with BMIs greater than or equal to 28. The greatest apparent effect of BMI on anti-HPV responses was observed with respect to HPV-16 and HPV-18, for which girls with a BMI  $\geq 28$  (GMT = 2531, 95% CI 1586 to 4040 for HPV-16 and GMT = 538, 95% CI 320 to 903 for HPV-18) appeared to have lower responses than girls with a BMI  $< 28$  (GMT = 5195, 95% CI 4654 to 5800 for HPV-16 and GMT = 1182, 95% CI 1065 to 1313 for HPV-18).

A secondary immunogenicity objective of the study was to describe the persistence of the immune response. One year postcompletion of the vaccination regimen (month 18),  $\geq 91.5\%$  of all vaccine recipients in the per-protocol population remained seropositive, regardless of gender (Table 4). In both boys and girls, GMTs at month 18 were approximately 4- to 7-fold lower than the GMTs observed at month 7.

**Safety.** Adverse experiences were common among both vaccine and placebo recipients. Table 5 summarizes the observed

adverse experiences after each dose and across all vaccination visits. The proportion of subjects who reported one or more injection-site or systemic adverse experience tended to be higher after the first injection than after subsequent injections, regardless of vaccination group.

A comparison of the vaccine and placebo groups across all vaccination visits showed that a significantly higher proportion of subjects in the quadrivalent HPV vaccine group reported injection-site adverse experiences days 1 to 5 after any vaccination than in the non-aluminum-containing placebo group (Table 5). Significantly higher percentages of subjects in the quadrivalent HPV vaccine group reported injection-site erythema, pain and swelling days 1 to 5 across all vaccination visits compared with the non-aluminum-containing placebo group ( $P < 0.001$ ).

The most common systemic adverse experiences reported were headache, fever and pharyngeal pain. There was no significant difference between vaccination groups with regard to the proportion of subjects who reported specific systemic adverse experiences prompted for on the vaccination report card (muscle/joint pain, headaches, rashes, hives, and diarrhea) days 1 to 15 across all vaccination visits.

The proportion of subjects who reported an elevated temperature within 5 days across all vaccination visits was not significantly different between subjects who received the quadrivalent HPV vaccine compared with subjects who received placebo (7.2 vs. 6.6%  $P = 0.638$ ; Table 5). Most fevers were low grade (maximum temperature below 102°F or 38.9°C).

Overall, 5 serious adverse experiences were reported through month 18, all of which occurred among the quadrivalent HPV vaccine recipients. None of these serious adverse experiences was judged by the investigator to be vaccine-related. Two of these serious adverse experiences occurred 6 days and 2 days, respectively, after the first injection: acute renal failure (subject recovered and discontinued from study); and insulin dependent diabetes mellitus. Three occurred 2 days, 11 days and 3 days, respectively, after the second injection: localized infection; anemia and dysfunctional uterine bleeding; and appendicitis. Two subjects in the quadrivalent HPV vaccine group and none in the placebo group discontinued treatment due to a nonserious vaccine-related



**TABLE 5.** Adverse Experience Summary Days 1–15 Postdose 1, 2 and 3 and Across All Vaccinations

	Postdose 1		Postdose 2		Postdose 3		Across All Vaccinations	
	Vaccine	Non-Aluminum Placebo	Vaccine	Non-Aluminum Placebo	Vaccine	Non-Aluminum Placebo	Vaccine	Non-Aluminum Placebo
Subjects with follow-up	1165	584	1139	564	1120	559	1165	584
No. (%) <sup>a</sup> of subjects								
With 1 or more AE	779 (66.9)	312 (53.4)	627 (55.0)	200 (35.5)	577 (51.5)	191 (34.2)	963 (82.7)	392 (67.1)
Injection-site AE	663 (56.9)	198 (33.9)	555 (48.7)	131 (23.2)	517 (46.2)	137 (24.5)	877 (75.3)	292 (50.0)
Erythema <sup>†</sup>	91 (7.8)	42 (7.2)	105 (9.2)	31 (5.5)	123 (11.0)	30 (5.4)	237 (20.3)	77 (13.2) <sup>‡</sup>
Pain <sup>†</sup>	623 (53.5)	180 (30.8)	532 (46.7)	114 (20.2)	494 (44.1)	124 (22.2)	853 (73.2)	265 (45.4) <sup>‡</sup>
Swelling <sup>†</sup>	91 (7.8)	27 (4.6)	106 (9.3)	13 (2.3)	135 (12.1)	19 (3.4)	241 (20.7)	45 (7.7) <sup>‡</sup>
Systemic AE	377 (32.4)	199 (34.1)	202 (17.7)	97 (17.2)	168 (15.0)	84 (15.0)	541 (46.4)	260 (44.5)
With serious AE	2 (0.2)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)	0 (0.0)
With serious vaccine-related AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever								
Subjects with follow-up	1153	574	1121	554	1105	552	1157	579
<100° F or normal <sup>†</sup>	1122 (97.3)	557 (97.0)	1092 (97.4)	540 (97.5)	1075 (97.3)	538 (97.5)	1074 (92.8)	541 (93.4)
≥100° F <sup>†</sup>	31 (2.7)	17 (3.0)	29 (2.6)	14 (2.5)	30 (2.7)	14 (2.5)	83 (7.2)	38 (6.6) <sup>§</sup>

<sup>a</sup>Percentages are calculated based on the number of subjects with follow-up.

<sup>†</sup>Adverse experiences reported days 1 to 5 following any vaccination visit.

<sup>‡</sup> $P < 0.001$ , for comparison of vaccination groups across all vaccination visits.

<sup>§</sup> $P = 0.638$ , for comparison of vaccination groups across all vaccination visits.

AE indicates adverse experience.

adverse experience. The reasons were injection-site swelling, whereby the subject discontinued treatment after receiving the second dose of quadrivalent vaccine; and injection-site pain, whereby the subject discontinued treatment after receiving the first dose of quadrivalent vaccine. Both subjects continued in the study for follow-up only. Through month 18, the proportions of subjects reporting new medical conditions were comparable between the 2 vaccination groups. In both groups, the most common new condition was influenza.

Regardless of vaccination group, a higher proportion of girls than boys reported adverse experiences, although no formal comparisons between genders were performed. The adverse experience findings in boys versus girls were generally comparable to those observed when considering subjects by vaccination group.

## DISCUSSION

Administration of a quadrivalent HPV vaccine to 9- to 15-year-olds was generally safe and well tolerated. A larger proportion of subjects who received the quadrivalent vaccine experienced injection-site adverse experiences compared with placebo subjects. However, few subjects discontinued vaccination because of an adverse experience. In this age group, the quadrivalent HPV vaccine was highly immunogenic and persistent immune responses were observed through 1-year postdose 3. In this study, and in a previous study,<sup>26</sup> the magnitude of anti-HPV responses varied with age at first vaccination, with the younger cohort having the most robust vaccine-induced anti-HPV responses. Vaccine-induced responses in 9- to 15-year olds were substantially higher than the vaccine-induced responses observed in 16- to 23-year-old women, the age group in whom 100% prophylactic efficacy of the vaccine has been demonstrated.<sup>18,19,22</sup> In young women, the efficacy and immunogenicity of this quadrivalent vaccine have been demonstrated to persist

through at least 5 years.<sup>21</sup> Thus, administration of quadrivalent HPV vaccine to young adolescents should similarly induce protective efficacy.

An expected drop in anti-HPV responses was observed between month 7 (1-month postdose 3) and month 18. In women aged 16 to 23, vaccine-induced anti-HPV responses have been shown to decline postvaccination, plateau between months 18 and 24 and remain stable through 5 years.<sup>20,21</sup> Additional data are needed to determine if the anti-HPV responses in 9- to 15-year olds plateau in a similar manner. There is no known immune correlate of protection for HPV. The vaccine-induced immune response appears highest for HPV-16; however, direct comparisons of the relative immunogenicity of the 4 VLP components cannot be made from the absolute titers, as the titers for each of the reference sera for the individual assays are not identical. The serology assays used in these studies measured HPV antibody titers in a competitive format whereby serum antibodies compete with HPV type-specific mouse mAbs to neutralizing epitopes present on each VLP.<sup>20</sup> The scale of the competitive immune response is dependent upon the particular attributes of the mAbs and the epitope that they recognize.

Ideally, prophylactic vaccines should be administered to populations immediately before their entry into the period of greatest risk for acquisition of the infection targeted by the vaccine. This principle must take into account the available data regarding the length of the risk period and the known duration of protection of the vaccine. Implementation of public health policy related to HPV vaccination must address 2 fundamental issues: 1) the optimal age for vaccination; and 2) whether vaccination should be limited to girls and women, or offered to both genders. The first 5 to 10 years following sexual debut represent the period of highest risk for acquisition of HPV infection.<sup>8–10</sup> In many countries, most adolescents will have experienced sexual debut by age 16 years. In

the United States, 7.9% of 14-year-old students participating in a population-based survey reported having already experienced sexual debut.<sup>11</sup> Thus, prophylactic HPV vaccination campaigns should be initiated before this age. While implementation of HPV vaccination campaigns in adolescents is reasonable, limited information regarding the safety, immunogenicity and duration of efficacy of quadrivalent HPV vaccine in this age group has been available. The results of the current study show that the vaccine is durable for up to 12 months postdose 3.

The question of whether HPV vaccination should be administered to girls and women, or to the population as a whole must be considered in the context of the epidemiology of HPV disease and previous experiences with implementation of new vaccines. HPV infection in men is common. Men are the primary vector for transmission of HPV to women. Over 10% of men will acquire a case of detectable genital warts during their lifetime.<sup>5</sup> Among men having sex with men, the incidence of anal cancer approaches the incidence observed for cervical cancer in settings where Pap testing is not routinely available.<sup>29</sup> Thus, men could derive significant benefit from HPV vaccination.

The optimal population benefit of vaccination is achieved through induction of herd immunity, defined as the induction of protective immunity in a sufficient proportion of the population such that unvaccinated subjects are protected because they are not exposed to the pathogen targeted by the vaccine.<sup>30</sup> The experience of rubella vaccination for the prevention of congenital rubella syndrome (CRS) in the United Kingdom demonstrated the value of universal vaccination to prevent serious infection-related diseases that affects only one gender. While both men and women can be infected by rubella, CRS can only occur as a consequence of infection in women because CRS is caused by infection of the fetus in utero. Rubella vaccination programs in the United Kingdom initially targeted girls only but was later changed to gender-neutral vaccination. This transition occurred because it was not possible to vaccinate 100% of women, the large reservoir of infected men precluded the development of herd immunity, and epidemics of infection in young adults invariably led to infection of pregnant women and spikes in the incidence of CRS. The eradication of CRS in the United Kingdom occurred only after a universal vaccination policy was adopted. HPV is highly prevalent in the sexually active population. Thus, universal vaccination is highly likely to lead to a more rapid reduction in the burden of HPV disease than gender-specific vaccination.

Together, these factors suggest that HPV vaccination programs should be gender neutral. However, the efficacy of prophylactic HPV vaccines in boys and men has yet to be determined. The results of the current study provide additional information on the safety and immunogenicity of the quadrivalent HPV vaccine in boys. In the study, vaccine-induced anti-HPV levels in boys were noninferior (and, in fact, numerically superior) to those observed in girls. The adverse experience profiles in boys and girls were comparable. The similar GMTs and seroconversion of rates of boys compared with girls and 16- to 23-year-old women<sup>26</sup> suggests that prophylactic HPV vaccination will induce durable pro-

TECTIVE efficacy in boys and men. A formal efficacy study is ongoing to definitively evaluate vaccine efficacy in men with respect to genital warts, penile and anal cancer.

## CONCLUSION

The current study demonstrates that administration of quadrivalent HPV-6/11/16/18 L1 VLP vaccine to 9- to 15-year-old boys and girls is highly immunogenic, provides durable immunity through 1 year postvaccination and is generally well tolerated. These results further support the implementation of gender neutral HPV vaccination program to eradicate cancers, precancerous lesions and genital warts caused by vaccine HPV types.

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# **EXHIBIT 259**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use GARDASIL 9 safely and effectively. See full prescribing information for GARDASIL 9.

**GARDASIL®9**

(Human Papillomavirus 9-valent Vaccine, Recombinant)  
Suspension for intramuscular injection

Initial U.S. Approval: 2014

**RECENT MAJOR CHANGES**

Indications and Usage, Girls and Women (1.1) 06/2020  
Indications and Usage, Boys and Men (1.2) 06/2020  
Indications and Usage, Limitations of Use and Effectiveness (1.3) 06/2020

**INDICATIONS AND USAGE**

GARDASIL 9 is a vaccine indicated in girls and women 9 through 45 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58. (1.1)
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11. (1.1)

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS). (1.1)
- Cervical intraepithelial neoplasia (CIN) grade 1. (1.1)
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3. (1.1)
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3. (1.1)
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. (1.1)

GARDASIL 9 is indicated in boys and men 9 through 45 years of age for the prevention of the following diseases:

- Anal, oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58. (1.2)
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11. (1.2)

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. (1.2)

The oropharyngeal and head and neck cancer indication is approved under accelerated approval based on effectiveness in preventing HPV-related anogenital disease. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial (1).

**Limitations of Use and Effectiveness:**

- Vaccination with GARDASIL 9 does not eliminate the necessity for vaccine recipients to undergo screening for cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers as recommended by a health care provider. (1.3, 17)
- GARDASIL 9 has not been demonstrated to provide protection against disease caused by:
  - HPV types not covered by the vaccine
  - HPV types to which a person has previously been exposed through sexual activity. (1.3)
- Not all vulvar, vaginal, anal, oropharyngeal and other head and neck cancers are caused by HPV, and GARDASIL 9 protects only against those vulvar, vaginal, anal, oropharyngeal and other head

and neck cancers caused by HPV 16, 18, 31, 33, 45, 52, and 58. (1.3)

- GARDASIL 9 is not a treatment for external genital lesions; cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers; CIN; VIN; VaIN; or AIN. (1.3)
- Vaccination with GARDASIL 9 may not result in protection in all vaccine recipients. (1.3)

**DOSAGE AND ADMINISTRATION**

**For intramuscular administration only. (2)**

Each dose of GARDASIL 9 is 0.5-mL

Administer GARDASIL 9 as follows: (2.1)

Age	Regimen	Schedule
9 through 14 years	2-dose	0, 6 to 12 months*
	3-dose	0, 2, 6 months
15 through 45 years	3-dose	0, 2, 6 months

\*If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose. (14.2 and 14.6)

**DOSAGE FORMS AND STRENGTHS**

- 0.5-mL suspension for injection as a single-dose vial and prefilled syringe. (3, 11)

**CONTRAINDICATIONS**

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL 9 or GARDASIL®. (4, 11)

**WARNINGS AND PRECAUTIONS**

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. (5.1)

**ADVERSE REACTIONS**

The most common (≥10%) local and systemic adverse reactions reported:

- In girls and women 16 through 26 years of age: injection-site pain (89.9%), injection-site swelling (40.0%), injection-site erythema (34.0%) and headache (14.6%). (6.1)
- In girls 9 through 15 years of age: injection-site pain (89.3%), injection-site swelling (47.8%), injection-site erythema (34.1%) and headache (11.4%). (6.1)
- In boys and men 16 through 26 years of age: injection-site pain (63.4%), injection-site swelling (20.2%) and injection-site erythema (20.7%). (6.1)
- In boys 9 through 15 years of age: injection-site pain (71.5%), injection-site swelling (26.9%), and injection-site erythema (24.9%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

- See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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**FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE****1.1 Girls and Women**

GARDASIL®9 is a vaccine indicated in girls and women 9 through 45 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

**1.2 Boys and Men**

GARDASIL 9 is indicated in boys and men 9 through 45 years of age for the prevention of the following diseases:

- Anal, oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

The oropharyngeal and head and neck cancer indication is approved under accelerated approval based on effectiveness in preventing HPV-related anogenital disease [see *Clinical Studies*, (14.4)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**1.3 Limitations of Use and Effectiveness**

- Vaccination with GARDASIL 9 does not eliminate the necessity for vaccine recipients to undergo screening for cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers as recommended by a health care provider.
- GARDASIL 9 has not been demonstrated to provide protection against disease caused by:
  - HPV types not covered by the vaccine [see *Description* (11)],
  - HPV types to which a person has previously been exposed through sexual activity.
- Not all vulvar, vaginal, anal, oropharyngeal and other head and neck cancers are caused by HPV, and GARDASIL 9 protects only against those vulvar, vaginal, anal, oropharyngeal and other head and neck cancers caused by HPV 16, 18, 31, 33, 45, 52, and 58.
- GARDASIL 9 is not a treatment for external genital lesions; cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers; CIN; VIN; VaIN; or AIN.
- Vaccination with GARDASIL 9 may not result in protection in all vaccine recipients.

## 2 DOSAGE AND ADMINISTRATION

For intramuscular use only

### 2.1 Dosage

Each dose of GARDASIL 9 is 0.5-mL.

Administer GARDASIL 9 as follows:

Age	Regimen	Schedule
9 through 14 years	2-dose	0, 6 to 12 months*
	3-dose	0, 2, 6 months
15 through 45 years	3-dose	0, 2, 6 months

\*If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose. [See *Clinical Studies (14.2 and 14.6)*.]

### 2.2 Method of Administration

- Do not dilute or mix GARDASIL 9 with other vaccines.
- Shake well immediately before use to maintain suspension of the vaccine.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the product if particulates are present or if it appears discolored. After thorough agitation, GARDASIL 9 is a white cloudy liquid.
- Administer intramuscularly in the deltoid or anterolateral area of the thigh.
- Observe patients for 15 minutes after administration [see *Warnings and Precautions (5)*].

#### Single-Dose Vial Use

Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe and use promptly. Discard vial after use.

#### Prefilled Syringe Use

This package does not contain a needle. Shake well before use. Attach a needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol. Discard syringe after use.

### 2.3 Administration of GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL®

Safety and immunogenicity were assessed in individuals who completed a three-dose vaccination series with GARDASIL 9 and had previously completed a three-dose vaccination series with GARDASIL [see *Adverse Reactions (6.1)* and *Clinical Studies (14.5)*]. Studies using a mixed regimen of HPV vaccines to assess interchangeability were not performed for GARDASIL 9.

## 3 DOSAGE FORMS AND STRENGTHS

GARDASIL 9 is a suspension for intramuscular administration available in 0.5-mL single-dose vials and prefilled syringes. See *Description (11)* for the complete listing of ingredients.

## 4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL 9 or GARDASIL [see *Description (11)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Syncope

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

## 5.2 Managing Allergic Reactions

Appropriate medical treatment and supervision must be readily available in case of anaphylactic reactions following the administration of GARDASIL 9.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of GARDASIL 9 was evaluated in seven clinical studies that included 15,703 individuals who received at least one dose of GARDASIL 9 and had safety follow-up. Study 1 and Study 3 also included 7,378 individuals who received at least one dose of GARDASIL as a control and had safety follow-up. The vaccines were administered on the day of enrollment and the subsequent doses administered approximately two and six months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL 9 or GARDASIL.

The individuals who were monitored using VRC-aided surveillance included 9,097 girls and women 16 through 26 years of age, 1,394 boys and men 16 through 26 years of age, and 5,212 girls and boys 9 through 15 years of age (3,436 girls and 1,776 boys) at enrollment who received GARDASIL 9; and 7,078 girls and women 16 through 26 years of age and 300 girls 9 through 15 years of age at enrollment who received GARDASIL. The race distribution of the integrated safety population for GARDASIL 9 was similar between girls and women 16 through 26 years of age (56.8% White; 25.2% Other Races or Multiracial; 14.1% Asian; 3.9% Black), girls and boys 9 through 15 years of age (62.0% White; 19.2% Other Races or Multiracial; 13.5% Asian; 5.4% Black), and boys and men 16 through 26 years of age (62.1% White; 22.6% Other Races or Multiracial; 9.8% Asian; 5.5% Black). The safety of GARDASIL 9 was compared directly to the safety of GARDASIL in two studies (Study 1 and Study 3) for which the overall race distribution of the GARDASIL cohorts (57.0% White; 26.3% Other Races or Multiracial; 13.6% Asian; 3.2% Black) was similar to that of the GARDASIL 9 cohorts.

Safety of GARDASIL 9 in individuals 27 through 45 years of age is inferred from the safety data of GARDASIL in individuals 9 through 45 years of age and GARDASIL 9 in individuals 9 through 26 years of age.

#### *Injection-Site and Systemic Adverse Reactions*

Injection-site reactions (pain, swelling, and erythema) and oral temperature were solicited using VRC-aided surveillance for five days after each injection of GARDASIL 9 during the clinical studies. The rates and severity of these solicited adverse reactions that occurred within five days following each dose of GARDASIL 9 compared with GARDASIL in Study 1 (girls and women 16 through 26 years of age) and Study 3 (girls 9 through 15 years of age) are presented in Table 1. Among subjects who received GARDASIL 9, the rates of injection-site pain were approximately equal across the three reporting time periods. Rates of injection-site swelling and injection-site erythema increased following each successive dose of GARDASIL 9. Recipients of GARDASIL 9 had numerically higher rates of injection-site reactions compared with recipients of GARDASIL.

**Table 1: Rates (%) and Severity of Solicited Injection-Site and Systemic Adverse Reactions Occurring within Five Days of Each Vaccination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)**

	GARDASIL 9				GARDASIL			
	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose
<b>Girls and Women 16 through 26 Years of Age</b>								
<b>Injection-Site Adverse Reactions</b>	<b>N=7069</b>	<b>N=6997</b>	<b>N=6909</b>	<b>N=7071</b>	<b>N=7076</b>	<b>N=6992</b>	<b>N=6909</b>	<b>N=7078</b>
Pain, Any	70.7	73.5	71.6	89.9	58.2	62.2	62.6	83.5
Pain, Severe	0.7	1.7	2.6	4.3	0.4	1.0	1.7	2.6
Swelling, Any	12.5	23.3	28.3	40.0	9.3	14.6	18.7	28.8
Swelling, Severe	0.6	1.5	2.5	3.8	0.3	0.5	1.0	1.5
Erythema, Any	10.6	18.0	22.6	34.0	8.1	12.9	15.6	25.6
Erythema, Severe	0.2	0.5	1.1	1.6	0.2	0.2	0.4	0.8
<b>Systemic Adverse Reactions</b>	<b>n=6995</b>	<b>n=6913</b>	<b>n=6743</b>	<b>n=7022</b>	<b>n=7003</b>	<b>n=6914</b>	<b>n=6725</b>	<b>n=7024</b>
Temperature $\geq 100^{\circ}\text{F}$	1.7	2.6	2.7	6.0	1.7	2.4	2.5	5.9
Temperature $\geq 102^{\circ}\text{F}$	0.3	0.3	0.4	1.0	0.2	0.3	0.3	0.8
<b>Girls 9 through 15 Years of Age</b>								
<b>Injection-Site Adverse Reactions</b>	<b>N=300</b>	<b>N=297</b>	<b>N=296</b>	<b>N=299</b>	<b>N=299</b>	<b>N=299</b>	<b>N=294</b>	<b>N=300</b>
Pain, Any	71.7	71.0	74.3	89.3	66.2	66.2	69.4	88.3
Pain, Severe	0.7	2.0	3.0	5.7	0.7	1.3	1.7	3.3
Swelling, Any	14.0	23.9	36.1	47.8	10.4	17.7	25.2	36.0
Swelling, Severe	0.3	2.4	3.7	6.0	0.7	2.7	4.1	6.3
Erythema, Any	7.0	15.5	21.3	34.1	9.7	14.4	18.4	29.3
Erythema, Severe	0	0.3	1.4	1.7	0	0.3	1.7	2.0
<b>Systemic Adverse Reactions</b>	<b>n=300</b>	<b>n=294</b>	<b>n=295</b>	<b>n=299</b>	<b>n=299</b>	<b>n=297</b>	<b>n=291</b>	<b>n=300</b>
Temperature $\geq 100^{\circ}\text{F}$	2.3	1.7	3.0	6.7	1.7	1.7	0	3.3
Temperature $\geq 102^{\circ}\text{F}$	0	0.3	1.0	1.3	0.3	0.3	0	0.7

The data for girls and women 16 through 26 years of age are from Study 1 (NCT00543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498).

N=number of subjects vaccinated with safety follow-up

n=number of subjects with temperature data

Pain, Any=mild, moderate, severe or unknown intensity

Pain, Severe=incapacitating with inability to work or do usual activity

Swelling, Any=any size or size unknown

Swelling, Severe=maximum size greater than 2 inches

Erythema, Any=any size or size unknown

Erythema, Severe=maximum size greater than 2 inches

Unsolicited injection-site and systemic adverse reactions (assessed as vaccine-related by the investigator) observed among recipients of either GARDASIL 9 or GARDASIL in Studies 1 and 3 at a frequency of at least 1% are shown in Table 2. Few individuals discontinued study participation due to adverse experiences after receiving either vaccine (GARDASIL 9 = 0.1% vs. GARDASIL <0.1%).

**Table 2: Rates (%) of Unsolicited Injection-Site and Systemic Adverse Reactions Occurring among  $\geq 1.0\%$  of Individuals after Any Vaccination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)**

	Girls and Women 16 through 26 Years of Age		Girls 9 through 15 Years of Age	
	GARDASIL 9 N=7071	GARDASIL N=7078	GARDASIL 9 N=299	GARDASIL N=300
<b>Injection-Site Adverse Reactions (1 to 5 Days Post-Vaccination, Any Dose)</b>				
Pruritus	5.5	4.0	4.0	2.7
Bruising	1.9	1.9	0	0
Hematoma	0.9	0.6	3.7	4.7
Mass	1.3	0.6	0	0
Hemorrhage	1.0	0.7	1.0	2.0
Induration	0.8	0.2	2.0	1.0
Warmth	0.8	0.5	0.7	1.7
Reaction	0.6	0.6	0.3	1.0
<b>Systemic Adverse Reactions (1 to 15 Days Post-Vaccination, Any Dose)</b>				
Headache	14.6	13.7	11.4	11.3
Pyrexia	5.0	4.3	5.0	2.7
Nausea	4.4	3.7	3.0	3.7
Dizziness	3.0	2.8	0.7	0.7
Fatigue	2.3	2.1	0	2.7
Diarrhea	1.2	1.0	0.3	0
Oropharyngeal pain	1.0	0.6	2.7	0.7
Myalgia	1.0	0.7	0.7	0.7
Abdominal pain, upper	0.7	0.8	1.7	1.3
Upper respiratory tract infection	0.1	0.1	0.3	1.0

The data for girls and women 16 through 26 years of age are from Study 1 (NCT00543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498).

N=number of subjects vaccinated with safety follow-up

In an uncontrolled clinical trial with 639 boys and 1,878 girls 9 through 15 years of age (Study 2), the rates and severity of solicited adverse reactions following each dose of GARDASIL 9 were similar between boys and girls. Rates of solicited and unsolicited injection-site and systemic adverse reactions in boys 9 through 15 years of age were similar to those among girls 9 through 15 years of age. Solicited and unsolicited adverse reactions reported by boys in this study are shown in Table 3.

In another uncontrolled clinical trial with 1,394 boys and men and 1,075 girls and women 16 through 26 years of age (Study 7), the rates of solicited and unsolicited adverse reactions following each dose of GARDASIL 9 among girls and women 16 through 26 years of age were similar to those reported in Study 1. Rates of solicited and unsolicited adverse reactions reported by boys and men 16 through 26 years of age in this study are shown in Table 3.



**Table 3: Rates (%) of Solicited and Unsolicited\* Injection-Site and Systemic Adverse Reactions among Boys 9 through 15 Years of Age and among Boys and Men 16 through 26 Years of Age Who Received GARDASIL 9 (Studies 2 and 7)**

	GARDASIL 9
<b>Boys and Men 16 through 26 Years of Age</b>	<b>N=1394</b>
<b>Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</b>	
Injection-Site Pain, Any	63.4
Injection-Site Pain, Severe	0.6
Injection-Site Erythema, Any	20.7
Injection-Site Erythema, Severe	0.4
Injection-Site Swelling, Any	20.2
Injection-Site Swelling, Severe	1.1
Oral Temperature $\geq 100.0^{\circ}\text{F}^{\dagger}$	4.4
Oral Temperature $\geq 102^{\circ}\text{F}$	0.6
<b>Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</b>	
Injection-Site Hypersensitivity	1.0
Injection-Site Pruritus	1.0
<b>Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)</b>	
Headache	7.3
Pyrexia	2.4
Fatigue	1.4
Dizziness	1.1
Nausea	1.0
<b>Boys 9 through 15 Years of Age</b>	<b>N=639</b>
<b>Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</b>	
Injection-Site Pain, Any	71.5
Injection-Site Pain, Severe	0.5
Injection-Site Erythema, Any	24.9
Injection-Site Erythema, Severe	1.9
Injection-Site Swelling, Any	26.9
Injection-Site Swelling, Severe	5.2
Oral Temperature $\geq 100.0^{\circ}\text{F}^{\dagger}$	10.4
Oral Temperature $\geq 102^{\circ}\text{F}$	1.4
<b>Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</b>	
Injection-Site Hematoma	1.3
Injection-Site Induration	1.1
<b>Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)</b>	
Headache	9.4
Pyrexia	8.9
Nausea	1.3

The data for GARDASIL 9 boys 9 through 15 years of age are from Study 2 (NCT00943722). The data for boys and men 16 through 26 years of age for GARDASIL 9 are from Study 7 (NCT01651949).

\*Unsolicited adverse reactions reported by  $\geq 1\%$  of individuals

N=number of subjects vaccinated with safety follow-up

<sup>†</sup>For oral temperature: number of subjects with temperature data for boys 9 through 15 years of age N=637; for boys and men 16 through 26 years of age N=1,386

Pain, Any=mild, moderate, severe or unknown intensity

Pain, Severe=incapacitating with inability to work or do usual activity

Swelling, Any=any size or size unknown

Swelling, Severe=maximum size greater than 2 inches

Erythema, Any=any size or size unknown

Erythema, Severe=maximum size greater than 2 inches

### *Serious Adverse Events in Clinical Studies*

Serious adverse events were collected throughout the entire study period (range one month to 48 months post-last dose) for the seven clinical studies for GARDASIL 9. Out of the 15,705 individuals who were administered GARDASIL 9 and had safety follow-up, 354 reported a serious adverse event; representing 2.3% of the population. As a comparison, of the 7,378 individuals who were administered GARDASIL and had safety follow-up, 185 reported a serious adverse event; representing 2.5% of the population. Four GARDASIL 9 recipients each reported at least one serious adverse event that was determined to be vaccine-related. The vaccine-related serious adverse reactions were pyrexia, allergy to vaccine, asthmatic crisis, and headache.

#### *Deaths in the Entire Study Population*

Across the clinical studies, ten deaths occurred (five each in the GARDASIL 9 and GARDASIL groups); none were assessed as vaccine-related. Causes of death in the GARDASIL 9 group included one automobile accident, one suicide, one case of acute lymphocytic leukemia, one case of hypovolemic septic shock, and one unexplained sudden death 678 days following the last dose of GARDASIL 9. Causes of death in the GARDASIL control group included one automobile accident, one airplane crash, one cerebral hemorrhage, one gunshot wound, and one stomach adenocarcinoma.

#### *Systemic Autoimmune Disorders*

In all of the clinical trials with GARDASIL 9 subjects were evaluated for new medical conditions potentially indicative of a systemic autoimmune disorder. In total, 2.2% (351/15,703) of GARDASIL 9 recipients and 3.3% (240/7,378) of GARDASIL recipients reported new medical conditions potentially indicative of systemic autoimmune disorders, which were similar to rates reported following GARDASIL, AAHS control, or saline placebo in historical clinical trials.

#### *Clinical Trials Experience for GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL*

A clinical study (Study 4) evaluated the safety of GARDASIL 9 in 12- through 26-year-old girls and women who had previously been vaccinated with three doses of GARDASIL. The time interval between the last injection of GARDASIL and the first injection of GARDASIL 9 ranged from approximately 12 to 36 months. Individuals were administered GARDASIL 9 or saline placebo and safety was evaluated using VRC-aided surveillance for 14 days after each injection of GARDASIL 9 or saline placebo in these individuals. The individuals who were monitored included 608 individuals who received GARDASIL 9 and 305 individuals who received saline placebo. Few (0.5%) individuals who received GARDASIL 9 discontinued due to adverse reactions. The vaccine-related adverse experiences that were observed among recipients of GARDASIL 9 at a frequency of at least 1.0% and also at a greater frequency than that observed among saline placebo recipients are shown in Table 4. Overall the safety profile was similar between individuals vaccinated with GARDASIL 9 who were previously vaccinated with GARDASIL and those who were naïve to HPV vaccination with the exception of numerically higher rates of injection-site swelling and erythema among individuals who were previously vaccinated with GARDASIL (Tables 1 and 4).

**Table 4: Rates (%) of Solicited and Unsolicited\* Injection-Site and Systemic Adverse Reactions among Individuals Previously Vaccinated with GARDASIL Who Received GARDASIL 9 or Saline Placebo (Girls and Women 12 through 26 Years of Age) (Study 4)**

	<b>GARDASIL 9 N=608</b>	<b>Saline Placebo N=305</b>
<b>Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</b>		
Injection-Site Pain	90.3	38.0
Injection-Site Erythema	42.3	8.5
Injection-Site Swelling	49.0	5.9
Oral Temperature $\geq 100.0^{\circ}\text{F}^{\dagger}$	6.5	3.0
<b>Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</b>		
Injection-Site Pruritus	7.7	1.3
Injection-Site Hematoma	4.8	2.3
Injection-Site Reaction	1.3	0.3
Injection-Site Mass	1.2	0.7
<b>Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)</b>		
Headache	19.6	18.0
Pyrexia	5.1	1.6
Nausea	3.9	2.0
Dizziness	3.0	1.6
Abdominal pain, upper	1.5	0.7
Influenza	1.2	1.0

The data for GARDASIL 9 and saline placebo are from Study 4 (NCT01047345).

\*Unsolicited adverse reactions reported by  $\geq 1\%$  of individuals

N=number of subjects vaccinated with safety follow-up

<sup>†</sup>For oral temperature: number of subjects with temperature data GARDASIL 9 N=604; Saline Placebo N=304

#### *Safety in Concomitant Use with Menactra and Adacel*

In Study 5, the safety of GARDASIL 9 when administered concomitantly with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] was evaluated in a randomized study of 1,241 boys (n = 620) and girls (n = 621) with a mean age of 12.2 years [see *Clinical Studies (14.7)*].

Of the 1,237 boys and girls vaccinated, 1,220 had safety follow-up for injection-site adverse reactions. The rates of injection-site adverse reactions were similar between the concomitant group and non-concomitant group (vaccination with GARDASIL 9 separated from vaccination with Menactra and Adacel by 1 month) with the exception of an increased rate of swelling reported at the injection site for GARDASIL 9 in the concomitant group (14.4%) compared to the non-concomitant group (9.4%). The majority of injection-site swelling adverse reactions were reported as being mild to moderate in intensity.

## **6.2 Postmarketing Experience**

The postmarketing adverse experiences were reported voluntarily from a population of uncertain size, therefore, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

The safety profile of GARDASIL 9 and GARDASIL are similar. The postmarketing safety experience with GARDASIL is relevant to GARDASIL 9 since the vaccines are manufactured similarly and contain the same L1 HPV proteins of four of the same HPV types.

### GARDASIL 9

In addition to the adverse reactions reported in the clinical studies, the following adverse experiences have been spontaneously reported during post-approval use of GARDASIL 9:

Gastrointestinal disorders: Vomiting  
Skin and subcutaneous tissue disorders: Urticaria

### GARDASIL

Additionally, the following postmarketing adverse experiences have been spontaneously reported for GARDASIL:

Blood and lymphatic system disorders: Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, lymphadenopathy.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolus.

Gastrointestinal disorders: Pancreatitis.

General disorders and administration site conditions: Asthenia, chills, death, malaise.

Immune system disorders: Autoimmune diseases, hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

Nervous system disorders: Acute disseminated encephalomyelitis, Guillain-Barré syndrome, motor neuron disease, paralysis, seizures, transverse myelitis.

Infections and infestations: Cellulitis.

Vascular disorders: Deep venous thrombosis.

## **7 DRUG INTERACTIONS**

### **7.1 Use with Systemic Immunosuppressive Medications**

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines [see *Use in Specific Populations* (8.6)].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### *Pregnancy Exposure Registry*

There is a pregnancy exposure registry to monitor pregnancy outcomes in women exposed to GARDASIL 9 during pregnancy. To enroll in or obtain information about the registry, call Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-800-986-8999.

#### *Risk Summary*

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are no adequate and well-controlled studies of GARDASIL 9 in pregnant women. Available human data do not demonstrate vaccine-associated increase in risk of major birth defects and miscarriages when GARDASIL 9 is administered during pregnancy.

In one developmental toxicity study, 0.5 mL of a vaccine formulation containing between 1 and 1.5 – fold of each of the 9 HPV antigen types was administered to female rats prior to mating and during gestation. In a second study, animals were administered a single human dose (0.5 mL) of GARDASIL 9 prior to mating, during gestation and during lactation. These animal studies revealed no evidence of harm to the fetus due to GARDASIL 9 [see *Data*].

#### *Data*

##### Human Data

In pre-licensure clinical studies of GARDASIL 9, women underwent pregnancy testing immediately prior to administration of each dose of GARDASIL 9 or control vaccine (GARDASIL). (Data from GARDASIL are relevant to GARDASIL 9 because both vaccines are manufactured using the same process and have overlapping compositions.) Subjects who were determined to be pregnant were instructed to defer vaccination until the end of their pregnancy. Despite this pregnancy screening regimen, some subjects were vaccinated very early in pregnancy before human chorionic gonadotropin (HCG) was detectable. An analysis was conducted to evaluate pregnancy outcomes for pregnancies with onset within 30 days before or after vaccination with GARDASIL 9 or GARDASIL. Among such pregnancies, there were 62 and 55 with known outcomes (excluding ectopic pregnancies and elective terminations) for GARDASIL 9 and GARDASIL, respectively, including 44 and 48 live births, respectively. The rates of pregnancies that resulted in a miscarriage were 27.4% (17/62) and 12.7% (7/55) in subjects

who received GARDASIL 9 or GARDASIL, respectively. The rates of live births with major birth defects were 0% (0/44) and 2.1% (1/48) in subjects who received GARDASIL 9 or GARDASIL, respectively.

A five-year pregnancy registry enrolled 2,942 women who were inadvertently exposed to GARDASIL within one month prior to the last menstrual period (LMP) or at any time during pregnancy, 2,566 of whom were prospectively followed. After excluding elective terminations (n=107), ectopic pregnancies (n=5) and those lost to follow-up (n=814), there were 1,640 pregnancies with known outcomes. Rates of miscarriage and major birth defects were 6.8% of pregnancies (111/1,640) and 2.4% of live born infants (37/1,527), respectively. These rates of assessed outcomes in the prospective population were consistent with estimated background rates.

In two postmarketing studies of GARDASIL (one conducted in the U.S., and the other in Nordic countries), pregnancy outcomes among subjects who received GARDASIL during pregnancy were evaluated retrospectively. Among the 1,740 pregnancies included in the U.S. study database, outcomes were available to assess the rates of major birth defects and miscarriage. Among the 499 pregnancies included in the Nordic study database, outcomes were available to assess the rates of major birth defects. In both studies, rates of assessed outcomes did not suggest an increased risk with the administration of GARDASIL during pregnancy.

#### Animal Data

Developmental toxicity studies were conducted in female rats. In one study, animals were administered 0.5 mL of a vaccine formulation containing between 1 and 1.5 –fold of each of the 9 HPV antigen types 5 and 2 weeks prior to mating, and on gestation day 6. In a second study, animals were administered a single human dose (0.5 mL) of GARDASIL 9, 5 and 2 weeks prior to mating, on gestation day 6, and on lactation day 7. No adverse effects on pre- and post-weaning development were observed. There were no vaccine-related fetal malformations or variations.

## **8.2 Lactation**

### *Risk Summary*

Available data are not sufficient to assess the effects of GARDASIL 9 on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GARDASIL 9 and any potential adverse effects on the breastfed child from GARDASIL 9 or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

## **8.4 Pediatric Use**

Safety and effectiveness have not been established in pediatric patients below 9 years of age.

## **8.5 Geriatric Use**

The safety and effectiveness of GARDASIL 9 have not been evaluated in a geriatric population, defined as individuals aged 65 years and over.

## **8.6 Immunocompromised Individuals**

The immunologic response to GARDASIL 9 may be diminished in immunocompromised individuals [see *Drug Interactions* (7.1)].

## **11 DESCRIPTION**

GARDASIL 9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations using recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS). The 9-valent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

GARDASIL 9 is a sterile suspension for intramuscular administration. Each 0.5-mL dose contains approximately 30 mcg of HPV Type 6 L1 protein, 40 mcg of HPV Type 11 L1 protein, 60 mcg of HPV Type 16 L1 protein, 40 mcg of HPV Type 18 L1 protein, 20 mcg of HPV Type 31 L1 protein, 20 mcg of HPV Type 33 L1 protein, 20 mcg of HPV Type 45 L1 protein, 20 mcg of HPV Type 52 L1 protein, and 20 mcg of HPV Type 58 L1 protein.

Each 0.5-mL dose of the vaccine also contains approximately 500 mcg of aluminum (provided as AAHS), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein, and water for injection. The product does not contain a preservative or antibiotics.

After thorough agitation, GARDASIL 9 is a white, cloudy liquid.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

HPV only infects human beings. Animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines may involve the development of humoral immune responses. Efficacy of GARDASIL 9 against anogenital diseases related to the vaccine HPV types in human beings is thought to be mediated by humoral immune responses induced by the vaccine, although the exact mechanism of protection is unknown.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

GARDASIL 9 has not been evaluated for the potential to cause carcinogenicity, genotoxicity or impairment of male fertility. GARDASIL 9 administered to female rats had no effects on fertility [see *Pregnancy (8.1)*].

## 14 CLINICAL STUDIES

In these studies, seropositive is defined as anti-HPV titer greater than or equal to the pre-specified serostatus cutoff for a given HPV type. Seronegative is defined as anti-HPV titer less than the pre-specified serostatus cutoff for a given HPV type. The serostatus cutoff is the antibody titer level above the assay's lower limit of quantification that reliably distinguishes sera samples classified by clinical likelihood of HPV infection and positive or negative status by previous versions of competitive Luminex Immunoassay (cLIA). The lower limits of quantification and serostatus cutoffs for each of the 9 vaccine HPV types are shown in Table 5 below. PCR positive is defined as DNA detected for a given HPV type. PCR negative is defined as DNA not detected for a given HPV type. The lower limit of detection for the multiplexed HPV PCR assays ranged from 5 to 34 copies per test across the 9 vaccine HPV types.

Table 5: Competitive Luminex Immunoassay (cLIA) Limits of Quantification and Serostatus Cutoffs for GARDASIL 9  
HPV Types

HPV Type	cLIA Lower Limit of Quantification (mMU*/mL)	cLIA Serostatus Cutoff (mMU*/mL)
HPV 6	16	30
HPV 11	6	16
HPV 16	12	20
HPV 18	8	24
HPV 31	4	10
HPV 33	4	8
HPV 45	3	8
HPV 52	3	8
HPV 58	4	8

\*mMU=milli-Merck Units

### 14.1 Efficacy and Effectiveness Data for GARDASIL

Efficacy and effectiveness of GARDASIL are relevant to GARDASIL 9 since the vaccines are manufactured similarly and contain four of the same HPV L1 VLPs.



*Individuals 16 through 26 Years of Age*

Efficacy of GARDASIL was assessed in five AAHS-controlled, double-blind, randomized clinical trials evaluating 24,596 individuals 16 through 26 years of age (20,541 girls and women and 4,055 boys and men). The results of these trials are shown in Table 6 below.

**Table 6: Analysis of Efficacy of GARDASIL in the PPE\* Population for Vaccine HPV Types**

Disease Endpoints	GARDASIL		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
16- through 26-Year-Old Girls and Women†					
HPV 16- or 18-related CIN 2/3 or AIS	8493	2	8464	112	98.2 (93.5, 99.8)
HPV 16- or 18-related VIN 2/3	7772	0	7744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3	7772	0	7744	9	100.0 (49.5, 100.0)
HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS	7864	9	7865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Warts	7900	2	7902	193	99.0 (96.2, 99.9)
HPV 6- and 11-related Genital Warts	6932	2	6856	189	99.0 (96.2, 99.9)
16- through 26-Year-Old Boys and Men					
External Genital Lesions HPV 6-, 11-, 16-, or 18-related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Condyloma	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)
HPV 6-, 11-, 16-, or 18-related Endpoint					
AIN 1/2/3	194	5	208	24	77.5 (39.6, 93.3)
AIN 2/3	194	3	208	13	74.9 (8.8, 95.4)
AIN 1	194	4	208	16	73.0 (16.3, 93.4)
Condyloma Acuminatum	194	0	208	6	100.0 (8.2, 100.0)
Non-acuminate	194	4	208	11	60.4 (-33.5, 90.8)

\*The PPE population consisted of individuals who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and who remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7).

†Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.

N=Number of individuals with at least one follow-up visit after Month 7

CI=Confidence Interval

Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.

Note 2: Table 6 does not include cases due to HPV types not covered by the vaccine.

AAHS = Amorphous Aluminum Hydroxyphosphate Sulfate, CIN = Cervical Intraepithelial Neoplasia, VIN = Vulvar Intraepithelial Neoplasia, VaIN=Vaginal Intraepithelial Neoplasia, PIN=Penile Intraepithelial Neoplasia, AIN=Anal Intraepithelial Neoplasia, AIS=Adenocarcinoma *In Situ*

In an extension study in females 16 through 26 years of age at enrollment, prophylactic efficacy of GARDASIL through Month 60 against overall cervical and genital disease related to HPV 6, 11, 16, and 18 was 100% (95% CI: 12.3%, 100%) compared to AAHS control.

An extension study in girls and women 16 through 23 years of age used national health care registries in Denmark, Iceland, Norway, and Sweden to monitor endpoint cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, or vaginal cancer among 2,650 girls and women 16 through 23 years of age at enrollment who were randomized to vaccination with GARDASIL. An interim analysis of the per-protocol effectiveness population included 1,902 subjects who completed the GARDASIL vaccination series within one year, were naïve to the relevant HPV type through 1 month post-dose 3, had no protocol violations, and had follow-up data available. The median follow-up from the first dose of vaccine was 6.7 years with a range of 2.8 to 8.4 years. At the time of interim analysis, no cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, or vaginal cancer were observed over a total of 5,765 person-years at risk.

*Girls and Boys 9 through 15 Years of Age*

An extension study of 614 girls and 565 boys 9 through 15 years of age at enrollment who were randomized to vaccination with GARDASIL actively followed subjects for endpoint cases of HPV 6-, 11-, 16-, or 18-related persistent infection, CIN (any grade), AIS, VIN, VaIN, cervical cancer, vulvar cancer,



vaginal cancer, and external genital lesions from the initiation of sexual activity or age 16 onwards. An interim analysis of the per-protocol effectiveness population included 246 girls and 168 boys who completed the GARDASIL vaccination series within one year, were seronegative to the relevant HPV type at initiation of the vaccination series, and had not initiated sexual activity prior to receiving the third dose of GARDASIL. The median follow-up from the first dose of vaccine was 7.2 years with a range of 0.5 to 8.5 years. At the time of interim analysis, no cases of persistent infection of at least 12 months' duration and no cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, VIN, VaIN, cervical cancer, vulvar cancer, vaginal cancer, or external genital lesions were observed over a total 1,105 person-years at risk. There were 4 cases of HPV 6-, 11-, 16-, or 18-related persistent infection of at least 6 months' duration, including 3 cases related to HPV 16 and 1 case related to HPV 6, none of which persisted to 12 months' duration.

#### *Individuals 27 through 45 Years of Age*

A clinical trial evaluated efficacy of GARDASIL in 3,253 women 27 through 45 years of age, based on a combined endpoint of HPV 6-, 11-, 16- or 18-related persistent infection, genital warts, vulvar and vaginal dysplastic lesions of any grade, CIN of any grade, AIS, and cervical cancer. These women were randomized 1:1 to receive either GARDASIL or AAHS control. The clinical trial was conducted in two phases: a base study and a long-term study extension. The per-protocol efficacy (PPE) population received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16 and 18) prior to dose 1 and remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7).

In the base study (median duration of follow-up of 3.5 years post-dose 3), the efficacy of GARDASIL against the combined incidence of HPV 6-, 11-, 16-, and 18-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, cervical dysplasia (any grade CIN), AIS and cervical cancer in the PPE population was 87.7% (95% CI: 75.4%, 94.6%). The efficacy estimate for the combined endpoint was driven primarily by prevention of persistent infection. The efficacy of GARDASIL against the combined incidence of HPV 6-, 11-, 16-, and 18-related genital warts or cervical dysplasia was 95.0% (95% CI: 68.7%, 99.9%) in the PPE population. While no statistically significant efficacy was demonstrated for GARDASIL in the base study for prevention of cervical intraepithelial neoplasia grades 2 and 3 (CIN 2/3), adenocarcinoma *in situ* (AIS) or cervical cancer related to HPV types 16 and 18, there was 1 case of CIN 2/3 observed in the GARDASIL group and 5 cases in the placebo group. The CIN 2 case in the GARDASIL group tested positive by PCR for HPV 16 and HPV 51.

In the long-term extension of this study, subjects from Colombia (n=600) randomized to the GARDASIL group in the base study were monitored for HPV 6-, 11-, 16-, and 18-related genital warts or cervical dysplasia. The median follow-up post-dose 3 was 8.9 years with a range of 0.1 to 10.1 years over a total of 3,518 person-years. During the long-term extension phase, no cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade) or genital warts were observed in the PPE population.

Effectiveness of GARDASIL in men 27 through 45 years of age is inferred from efficacy data in women 27 through 45 years of age as described above and supported by immunogenicity data from a clinical trial in which 150 men, 27 through 45 years of age, received a 3-dose regimen of GARDASIL (0, 2, 6 months). A cross-study analysis of per-protocol immunogenicity populations compared Month 7 anti-HPV 6, 11, 16, and 18 GMTs of these 27- through 45-year-old men (Study A) to those of 16- through 26-year old boys and men (Study B) in whom efficacy of GARDASIL had been established (see Table 6). GMT ratios (Study A/Study B) for HPV 6, 11, 16, and 18 were 0.82 (95%CI: 0.65, 1.03), 0.79 (95%CI: 0.66, 0.93), 0.91 (95%CI: 0.72, 1.13), and 0.74 (95%CI: 0.59, 0.92), respectively.

#### **14.2 Clinical Trials for GARDASIL 9**

Efficacy and/or immunogenicity of the 3-dose regimen of GARDASIL 9 were assessed in six clinical trials. Study 1 evaluated the efficacy of GARDASIL 9 to prevent HPV-related cervical, vulvar, and vaginal disease using GARDASIL as a comparator.

The analysis of efficacy for GARDASIL 9 was evaluated in the per-protocol efficacy (PPE) population of 16- through 26-year-old girls and women, who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, and were naïve to the relevant HPV type(s) by serology and PCR of cervicovaginal specimens prior to dose one and who remained PCR

negative for the relevant HPV type(s) through one month post-dose 3 (Month 7). Overall, approximately 52% of subjects were negative to all vaccine HPV types by both PCR and serology at Day 1.

The primary analysis of efficacy against HPV Types 31, 33, 45, 52, and 58 is based on a combined endpoint of Cervical Intraepithelial Neoplasia (CIN) 2, CIN 3, Adenocarcinoma *in situ* (AIS), invasive cervical carcinoma, Vulvar Intraepithelial Neoplasia (VIN) 2/3, Vaginal Intraepithelial Neoplasia (VaIN) 2/3, vulvar cancer, or vaginal cancer. Other endpoints evaluated include cervical, vulvar and vaginal disease of any grade, persistent infection, cytological abnormalities and invasive procedures. For all endpoints, the efficacy against the HPV Types 31, 33, 45, 52 and 58 in GARDASIL 9 was evaluated compared with GARDASIL. Efficacy of GARDASIL 9 against anal lesions caused by HPV Types 31, 33, 45, 52, and 58 was not assessed due to low incidence. Effectiveness of GARDASIL 9 against anal lesions was inferred from the efficacy of GARDASIL against anal lesions caused by HPV types 6, 11, 16 and 18 in men and antibody responses elicited by GARDASIL 9 against the HPV types covered by the vaccine.

Effectiveness against disease caused by HPV Types 6, 11, 16, and 18 was assessed by comparison of geometric mean titers (GMTs) of type-specific antibodies following vaccination with GARDASIL 9 with those following vaccination with GARDASIL (Study 1 and Study 3). The effectiveness of GARDASIL 9 in girls and boys 9 through 15 years old and in boys and men 16 through 26 years old was inferred based on a comparison of type-specific antibody GMTs to those of 16 through 26-year-old girls and women following vaccination with GARDASIL 9. Immunogenicity analyses were performed in the per-protocol immunogenicity (PPI) population consisting of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met pre-defined day range for serum collection for assessment of antibody response and were naïve [PCR negative (in girls and women 16 through 26 years of age; Studies 1 and 2) and seronegative (Studies 1, 2, 3, 5, 7 and 8)] to the relevant HPV type(s) prior to dose 1 and among 16- through 26-year-old girls and women (Studies 1 and 2) remained PCR negative to the relevant HPV type(s) through Month 7. Pre-defined day ranges for vaccinations were relative to Day 1 (dose 1). For the 3-dose schedule, dose 2 was at 2 months ( $\pm 3$  weeks) and dose 3 was at 6 months ( $\pm 4$  weeks). For the 2-dose schedule, dose 2 was at 6 or 12 months ( $\pm 4$  weeks). Pre-defined day range for serum collection for assessment of antibody response was 21 to 49 days after the last dose.

Study 1 evaluated immunogenicity of GARDASIL 9 and efficacy to prevent infection and disease caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in 16- through 26-year-old girls and women. Study 2 evaluated immunogenicity of GARDASIL 9 in girls and boys 9 through 15 years of age and women 16 through 26 years of age. Study 3 evaluated immunogenicity of GARDASIL 9 compared with GARDASIL in girls 9 through 15 years of age. Study 4 evaluated administration of GARDASIL 9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL. Study 5 evaluated GARDASIL 9 concomitantly administered with Menactra and Adacel in girls and boys 11 through 15 years of age. Together, these five clinical trials evaluated 12,233 individuals who received GARDASIL 9 (8,048 girls and women 16 through 26 years of age at enrollment with a mean age of 21.8 years; 2,927 girls 9 through 15 years of age at enrollment with a mean age of 11.9 years; and 1,258 boys 9 through 15 years of age at enrollment with a mean age of 11.9 years). Study 7 evaluated immunogenicity of GARDASIL 9 in boys and men, including 1,106 self-identified as heterosexual men (HM) and 313 self-identified as men having sex with men (MSM), 16 through 26 years of age at enrollment (mean ages 20.8 years and 22.2 years, respectively) and 1,101 girls and women 16 through 26 years of age at enrollment (mean age 21.3 years).

The race distribution of the 16- through 26-year-old girls and women in the clinical trials was as follows: 56.8% White; 25.2% Other; 14.1% Asian; and 3.9% Black. The race distribution of the 9- through 15-year-old girls in the clinical trials was as follows: 60.3% White; 19.3% Other; 13.5% Asian; and 7.0% Black. The race distribution of the 9- through 15-year-old boys in the clinical trials was as follows: 46.6% White; 34.3% Other; 13.3% Asian; and 5.9% Black. The race distribution of the 16- through 26-year-old boys and men in the clinical trials was as follows: 62.1% White; 22.6% Other; 9.8% Asian; and 5.5% Black.

One clinical trial (Study 8) assessed the 2-dose regimen of GARDASIL 9. Study 8 evaluated the immunogenicity of 2 doses of GARDASIL 9 in girls and boys 9 through 14 years of age and 3 doses of GARDASIL 9 in girls 9 through 14 years of age and women 16 through 26 years of age; (N=1,518; 753 girls; 451 boys and 314 women). The mean age for the girls and boys 9 through 14 years of age was 11.5

years; the mean age for girls and women 16 through 26 years of age was 21.0 years. In Study 8, the race distribution was as follows: 61.1% White; 16.3% Asian; 13.3% Other; and 8.9% Black.

### 14.3 Efficacy – HPV Types 31, 33, 45, 52 and 58 in Girls and Women 16 through 26 Years of Age

#### *Studies Supporting the Efficacy of GARDASIL 9 against HPV Types 31, 33, 45, 52, and 58*

The efficacy of GARDASIL 9 in 16- through 26-year-old girls and women was assessed in an active comparator-controlled, double-blind, randomized clinical trial (Study 1) that included a total of 14,204 women (GARDASIL 9 = 7,099; GARDASIL = 7,105) who were enrolled and vaccinated without pre-screening for the presence of HPV infection. Subjects were followed up with a median duration of 40 months (range 0 to 64 months) after the last vaccination.

The primary efficacy evaluation was conducted in the PPE population based on a composite clinical endpoint of HPV 31-, 33-, 45-, 52-, and 58-related cervical cancer, vulvar cancer, vaginal cancer, CIN 2/3 or AIS, VIN 2/3, and VaIN 2/3. Efficacy was further evaluated with the clinical endpoints of HPV 31-, 33-, 45-, 52-, and 58-related CIN 1, vulvar and vaginal disease of any grade, and persistent infection. In addition, the study also evaluated the impact of GARDASIL 9 on the rates of HPV 31-, 33-, 45-, 52-, and 58-related abnormal Papanicolaou (Pap) tests, cervical and external genital biopsy, and definitive therapy [including loop electrosurgical excision procedure (LEEP) and conization]. Efficacy for all endpoints was measured starting after the Month 7 visit.

GARDASIL 9 prevented HPV 31-, 33-, 45-, 52-, and 58-related persistent infection and disease and also reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58-related Pap test abnormalities, cervical and external genital biopsy, and definitive therapy (Table 7).

**Table 7: Analysis of Efficacy of GARDASIL 9 against HPV Types 31, 33, 45, 52, and 58 in the PPE\* Population of 16- through 26-Year-old Girls and Women (Study 1)**

Disease Endpoint	GARDASIL 9 N <sup>†</sup> =7099		GARDASIL N <sup>†</sup> =7105		GARDASIL 9 Efficacy % (95% CI)
	n <sup>‡</sup>	Number of cases	n <sup>‡</sup>	Number of cases	
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	6016	1	6017	30	96.7 (80.9, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related CIN 1	5948	1	5943	69	98.6 (92.4, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS	5948	1	5943	27	96.3 (79.5, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related Vulvar or Vaginal Disease	6009	1	6012	16	93.8 (61.5, 99.7)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥6 Months <sup>§</sup>	5939	26	5953	642	96.2 (94.4, 97.5)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months <sup>¶</sup>	5939	15	5953	375	96.1 (93.7, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap <sup>#</sup> Abnormality	5881	35	5882	462	92.6 (89.7, 94.8)
HPV 31-, 33-, 45-, 52-, 58-related Biopsy	6016	7	6017	222	96.9 (93.6, 98.6)
HPV 31-, 33-, 45-, 52-, 58-related Definitive Therapy <sup>‡</sup>	6012	4	6014	32	87.5 (65.7, 96.0)

\*The PPE population consisted of individuals who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 31, 33, 45, 52, and 58) prior to dose 1, and who remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7); data from Study 1 (NCT00543543).

<sup>†</sup>N=Number of individuals randomized to the respective vaccination group who received at least one injection

<sup>‡</sup>n=Number of individuals contributing to the analysis

<sup>§</sup>Persistent infection detected in samples from two or more consecutive visits at least six months apart

<sup>¶</sup>Persistent infection detected in samples from two or more consecutive visits over 12 months or longer

<sup>#</sup>Papanicolaou test

<sup>‡</sup>Including loop electrosurgical excision procedure (LEEP) and conization

CI=Confidence Interval

CIN=Cervical Intraepithelial Neoplasia, VIN=Vulvar Intraepithelial Neoplasia, VaIN=Vaginal Intraepithelial Neoplasia,

AIS=Adenocarcinoma *In Situ*, ASC-US=Atypical squamous cells of undetermined significance

HR=High Risk

#### 14.4 Effectiveness in Prevention of HPV-Related Oropharyngeal and Other Head and Neck Cancers

The effectiveness of GARDASIL 9 against oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, is based on the effectiveness of GARDASIL and GARDASIL 9 to prevent anogenital disease caused by HPV types covered by the vaccine [see *Clinical Studies* (14.1, 14.2, 14.3)].

#### 14.5 Immunogenicity of a 3-Dose Regimen

The minimum anti-HPV titer that confers protective efficacy has not been determined.

Type-specific immunoassays (i.e., cLIA) with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate. Immunogenicity was measured by (1) the percentage of individuals who were seropositive for antibodies against the relevant vaccine HPV type, and (2) the Geometric Mean Titer (GMT).

##### *Studies Supporting the Effectiveness of GARDASIL 9 against HPV Types 6, 11, 16, and 18*

Effectiveness of GARDASIL 9 against persistent infection and disease related to HPV Types 6, 11, 16, or 18 was inferred from non-inferiority comparisons in Study 1 (16- through 26-year-old girls and women) and Study 3 (9- through 15-year-old girls) of GMTs following vaccination with GARDASIL 9 with those following vaccination with GARDASIL. A low number of efficacy endpoint cases related to HPV types 6, 11, 16 and 18 in both vaccination groups precluded a meaningful assessment of efficacy using disease endpoints associated with these HPV types. The primary analyses were conducted in the per-protocol population, which included subjects who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, and were HPV-naïve. HPV-naïve individuals were defined as seronegative to the relevant HPV type(s) prior to dose 1 and among female subjects 16 through 26 years of age in Study 1 PCR negative to the relevant HPV type(s) in cervicovaginal specimens prior to dose 1 through Month 7.

Anti-HPV 6, 11, 16 and 18 GMTs at Month 7 for GARDASIL 9 among girls 9 through 15 years of age and young women 16 through 26 years of age were non-inferior to those among the corresponding populations for GARDASIL (Table 8). At least 99.7% of individuals included in the analyses for each HPV type became seropositive by Month 7.

**Table 8: Comparison of Immune Responses (Based on cLIA) Between GARDASIL 9 and GARDASIL for HPV Types 6, 11, 16, and 18 in the PPI\* Population of 9- through 26-Year-Old Girls and Women (Studies 1 and 3)**

Population	GARDASIL 9		GARDASIL		GARDASIL 9/ GARDASIL	
	N <sup>†</sup> (n <sup>‡</sup> )	GMT mMU <sup>§</sup> /mL	N <sup>†</sup> (n <sup>‡</sup> )	GMT mMU <sup>§</sup> /mL	GMT Ratio	(95% CI) <sup>†</sup>
<b>Anti-HPV 6</b>						
9- through 15-year-old girls	300 (273)	1679.4	300 (261)	1565.9	1.07	(0.93, 1.23)
16- through 26-year-old girls and women	6792 (3993)	893.1	6795 (3975)	875.2	1.02	(0.99, 1.06)
<b>Anti-HPV 11</b>						
9- through 15-year-old girls	300 (273)	1315.6	300 (261)	1417.3	0.93	(0.80, 1.08)
16- through 26-year-old girls and women	6792 (3995)	666.3	6795 (3982)	830.0	0.80	(0.77, 0.83)
<b>Anti-HPV 16</b>						
9- through 15-year-old girls	300 (276)	6739.5	300 (270)	6887.4	0.97	(0.85, 1.11)
16- through 26-year-old girls and women	6792 (4032)	3131.1	6795 (4062)	3156.6	0.99	(0.96, 1.03)
<b>Anti-HPV 18</b>						

Population	GARDASIL 9		GARDASIL		GARDASIL 9/ GARDASIL	
	N <sup>†</sup> (n <sup>‡</sup> )	GMT mMU <sup>§</sup> /mL	N <sup>†</sup> (n <sup>‡</sup> )	GMT mMU <sup>§</sup> /mL	GMT Ratio	(95% CI) <sup>¶</sup>
9- through 15-year-old girls	300 (276)	1956.6	300 (269)	1795.6	1.08	(0.91, 1.29)
16- through 26-year-old girls and women	6792 (4539)	804.6	6795 (4541)	678.7	1.19	(1.14, 1.23)

\*The PPI population consisted of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, were naïve (PCR negative [among 16- through 26-year old girls and women] and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, and among 16- through 26-year-old girls and women remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7). The data for 16- through 26-year-old girls and women are from Study 1 (NCT00543543), and the data for 9- through 15-year-old girls are from Study 3 (NCT01304498).

<sup>†</sup>N=Number of individuals randomized to the respective vaccination group who received at least one injection

<sup>‡</sup>n=Number of individuals contributing to the analysis

<sup>§</sup>mMU=milli-Merck Units

<sup>¶</sup>Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

CI=Confidence Interval

GMT=Geometric Mean Titer

cLIA=competitive Luminex Immunoassay

### *Study Supporting the Effectiveness of GARDASIL 9 against Vaccine HPV Types in 9- through 15-Year-Old Girls and Boys*

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 9- through 15-year-old girls and boys was inferred from non-inferiority comparison conducted in the PPI population in Study 2 of GMTs following vaccination with GARDASIL 9 among 9- through 15-year-old girls and boys with those among 16- through 26-year-old girls and women. Anti-HPV GMTs at Month 7 among 9- through 15-year-old girls and boys were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 9).

**Table 9: Comparison of Immune Responses (Based on cLIA) between the PPI\* Populations of 16- through 26-Year-Old Girls and Women, 9- through 15-Year-Old Girls, and 9- through 15-Year-Old Boys for All GARDASIL 9 Vaccine HPV Types (Study 2)**

Population	N <sup>†</sup>	n <sup>‡</sup>	GMT mMU <sup>§</sup> /mL	GMT Ratio relative to 16- through 26-year-old girls and women (95% CI) <sup>¶</sup>
<b>Anti-HPV 6</b>				
9- through 15-year-old girls	630	503	1703.1	1.89 (1.68, 2.12)
9- through 15-year-old boys	641	537	2083.4	2.31 (2.06, 2.60)
16- through 26-year-old girls and women	463	328	900.8	1
<b>Anti-HPV 11</b>				
9- through 15-year-old girls	630	503	1291.5	1.83 (1.63, 2.05)
9- through 15-year-old boys	641	537	1486.3	2.10 (1.88, 2.36)
16- through 26-year-old girls and women	463	332	706.6	1
<b>Anti-HPV 16</b>				
9- through 15-year-old girls	630	513	6933.9	1.97 (1.75, 2.21)
9- through 15-year-old boys	641	546	8683.0	2.46 (2.20, 2.76)
16- through 26-year-old girls and women	463	329	3522.6	1
<b>Anti-HPV 18</b>				
9- through 15-year-old girls	630	516	2148.3	2.43 (2.12, 2.79)
9- through 15-year-old boys	641	544	2855.4	3.23 (2.83, 3.70)
16- through 26-year-old girls and women	463	345	882.7	1
<b>Anti-HPV 31</b>				
9- through 15-year-old girls	630	506	1894.7	2.51 (2.21, 2.86)
9- through 15-year-old boys	641	543	2255.3	2.99 (2.63, 3.40)
16- through 26-year-old girls and women	463	340	753.9	1
<b>Anti-HPV 33</b>				



9- through 15-year-old girls	630	518	985.8	2.11 (1.88, 2.37)
9- through 15-year-old boys	641	544	1207.4	2.59 (2.31, 2.90)
16- through 26-year-old girls and women	463	354	466.8	1
<b>Anti-HPV 45</b>				
9- through 15-year-old girls	630	518	707.7	2.60 (2.25, 3.00)
9- through 15-year-old boys	641	547	912.1	3.35 (2.90, 3.87)
16- through 26-year-old girls and women	463	368	272.2	1
<b>Anti-HPV 52</b>				
9- through 15-year-old girls	630	517	962.2	2.21 (1.96, 2.49)
9- through 15-year-old boys	641	545	1055.5	2.52 (2.22, 2.84)
16- through 26-year-old girls and women	463	337	419.6	1
<b>Anti-HPV 58</b>				
9- through 15-year-old girls	630	516	1288.0	2.18 (1.94, 2.46)
9- through 15-year-old boys	641	544	1593.3	2.70 (2.40, 3.03)
16- through 26-year-old girls and women	463	332	590.5	1

\*The PPI population consisted of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, were naïve (PCR negative [among 16- through 26-year old girls and women] and seronegative) to the relevant HPV type(s) prior to dose 1 and among 16- through 26-year-old girls and women remained PCR negative to the relevant HPV types through one month post-dose 3 (Month 7). The data are from Study 2 (NCT00943722).

<sup>†</sup>N=Number of individuals randomized to the respective vaccination group who received at least one injection

<sup>‡</sup>n=Number of individuals contributing to the analysis

<sup>§</sup>mMU=milli-Merck Units

<sup>¶</sup>Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

cLIA=competitive Luminex Immunoassay

CI=Confidence Interval

GMT=Geometric Mean Titer

#### *Study Supporting the Effectiveness of GARDASIL 9 against Vaccine HPV Types in 16- through 26-Year-Old Boys and Men*

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 16- through 26-year-old boys and men was inferred from non-inferiority comparison conducted in the PPI population in Study 7 of GMTs following vaccination with GARDASIL 9 among 16- through 26-year-old HM with those among 16- through 26-year-old girls and women. Anti-HPV GMTs at Month 7 among 16- through 26-year-old HM were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 10). Study 7 also enrolled 313 16- through 26-year-old HIV-negative MSM. At Month 7, anti-HPV GMT ratios for MSM relative to HM ranged from 0.6 to 0.8, depending on HPV type. The GMT ratios for MSM relative to HM were generally similar to those previously observed in clinical trials with GARDASIL.

**Table 10: Comparison of Immune Responses (Based on cLIA) between the PPI\* Populations of 16- through 26-Year-Old Girls and Women and 16- through 26-Year-Old Boys and Men Self-Identified as Heterosexual (HM) for All GARDASIL 9 Vaccine HPV Types (Study 7)**

Population	N <sup>†</sup>	n <sup>‡</sup>	GMT mMU <sup>§</sup> /mL	GMT Ratio relative to 16- through 26-year- old girls and women (95% CI) <sup>¶</sup>
<b>Anti-HPV 6</b>				
16- through 26-year-old HM	1103	847	782.0	1.11 (1.02, 1.21)
16- through 26-year-old girls and women	1099	708	703.9	1
<b>Anti-HPV 11</b>				
16- through 26-year-old HM	1103	851	616.7	1.09 (1.00, 1.19)
16- through 26-year-old girls and women	1099	712	564.9	1
<b>Anti-HPV 16</b>				
16- through 26-year-old HM	1103	899	3346.0	1.20 (1.10, 1.30)
16- through 26-year-old girls and women	1099	781	2788.3	1
<b>Anti-HPV 18</b>				
16- through 26-year-old HM	1103	906	808.2	1.19 (1.08, 1.31)
16- through 26-year-old girls and women	1099	831	679.8	1
<b>Anti-HPV 31</b>				
16- through 26-year-old HM	1103	908	708.5	1.24 (1.13, 1.37)
16- through 26-year-old girls and women	1099	826	570.1	1
<b>Anti-HPV 33</b>				
16- through 26-year-old HM	1103	901	384.8	1.19 (1.10, 1.30)
16- through 26-year-old girls and women	1099	853	322.0	1
<b>Anti-HPV 45</b>				
16- through 26-year-old HM	1103	909	235.6	1.27 (1.14, 1.41)
16- through 26-year-old girls and women	1099	871	185.7	1
<b>Anti-HPV 52</b>				
16- through 26-year-old HM	1103	907	386.8	1.15 (1.05, 1.26)
16- through 26-year-old girls and women	1099	849	335.2	1
<b>Anti-HPV 58</b>				
16- through 26-year-old HM	1103	897	509.8	1.25 (1.14, 1.36)
16- through 26-year-old girls and women	1099	839	409.3	1

\*The PPI population consisted of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1. The data are from Study 7 (NCT01651949).

<sup>†</sup>Number of individuals randomized to the respective vaccination group who received at least one injection

<sup>‡</sup>Number of individuals contributing to the analysis

<sup>§</sup>mMU=milli-Merck Units

<sup>¶</sup>Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

cLIA=competitive Luminex Immunoassay

CI=Confidence Interval

GMT=Geometric Mean Titer

#### *Immune Response to GARDASIL 9 across All Clinical Trials*

Across all clinical trials, at least 99.5% of individuals included in the analyses for each of the nine vaccine HPV types became seropositive by Month 7. Anti-HPV GMTs at Month 7 among 9- through 15-year-old girls and boys and 16- through 26-year-old boys and men were comparable to anti-HPV responses among 16- through 26-year-old girls and women in the combined database of immunogenicity studies for GARDASIL 9.

#### *Persistence of Immune Response to GARDASIL 9*

The duration of immunity following a 3-dose schedule of vaccination with GARDASIL 9 has not been established. The peak anti-HPV GMTs for each vaccine HPV type occurred at Month 7. Proportions of individuals who remained seropositive to each vaccine HPV type at Month 24 were similar to the corresponding seropositive proportions at Month 7.

#### *Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL*

Study 4 evaluated the immunogenicity of 3 doses of GARDASIL 9 in 921 girls and women (12 through 26 years of age) who had previously been vaccinated with 3 doses of GARDASIL. Prior to enrollment in



the study, over 99% of subjects had received three injections of GARDASIL within a one year period. The time interval between the last injection of GARDASIL and the first injection of GARDASIL 9 ranged from approximately 12 to 36 months.

Seropositivity to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the per protocol population ranged from 98.3 to 100% by Month 7 in individuals who received GARDASIL 9. The anti-HPV 31, 33, 45, 52 and 58 GMTs for the population previously vaccinated with GARDASIL were 25-63% of the GMTs in the combined populations from Studies 1, 2, 3, and 5, who had not previously received GARDASIL, although the clinical relevance of these differences is unknown. Efficacy of GARDASIL 9 in preventing infection and disease related to HPV Types 31, 33, 45, 52, and 58 in individuals previously vaccinated with GARDASIL has not been assessed.

#### *Concomitant Use of Hormonal Contraceptives*

Among 7,269 female recipients of GARDASIL 9 (16 through 26 years of age), 60.2% used hormonal contraceptives during the vaccination period of clinical studies 1 and 2. Use of hormonal contraceptives did not appear to affect the type specific immune responses to GARDASIL 9.

#### **14.6 Immune Responses to GARDASIL 9 Using a 2-Dose Regimen in Individuals 9 through 14 Years of Age**

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 9- through 14-year-old girls and boys who received a 2-dose regimen was inferred from non-inferiority comparison conducted in the PPI population in Study 8 of GMTs following vaccination with GARDASIL 9 among 9- through 14-year-old girls and boys who received a 2-dose regimen (at 0, 6 months or 0, 12 months) with those among 16- through 26-year-old girls and women who received a 3-dose regimen (at 0, 2, 6 months). Anti-HPV GMTs at one month after the last dose among 9- through 14-year-old girls and boys who received 2 doses of GARDASIL 9 were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women who received 3 doses of GARDASIL 9 (Table 11).

One month following the last dose of the assigned regimen, between 97.9% and 100% of subjects across all groups became seropositive for antibodies against the 9 vaccine HPV types (Table 11).

In the same study, in girls and boys 9 through 14 years old, GMTs at one month after the last vaccine dose were numerically lower for some vaccine types after a 2-dose schedule than in girls 9 through 14 years old after a 3-dose schedule (HPV types 18, 31, 45, and 52 after 0, 6 months and HPV type 45 after 0, 12 months; Table 11). The clinical relevance of these findings is unknown.

Duration of immunity of a 2-dose schedule of GARDASIL 9 has not been established.

**Table 11: Summary of Anti-HPV cLIA Geometric Mean Titers in the PPI\* Population at One Month After the Last Vaccine Dose Among Subjects Who Received 2 Doses<sup>†</sup> or 3 Doses<sup>†</sup> of GARDASIL 9 (Study 8)**

Population (Regimen)	N	n	GMT mMU <sup>‡</sup> /mL	GMT Ratio relative to 3- dose regimen in 16- through 26-year-old girls and women (95% CI)
<b>Anti-HPV 6</b>				
9- to 14-year-old girls (0, 6) <sup>†</sup>	301	258	1657.9	2.15 (1.83, 2.53) <sup>§</sup>
9- to 14-year-old boys (0, 6) <sup>†</sup>	301	263	1557.4	2.02 (1.73, 2.36) <sup>§</sup>
9- to 14-year-old girls and boys (0, 12) <sup>†</sup>	300	257	2678.8	3.47 (2.93, 4.11) <sup>§</sup>
9- to 14-year-old girls (0, 2, 6) <sup>†</sup>	300	254	1496.1	1.94 (1.65, 2.29) <sup>¶</sup>
16- to 26-year-old women (0, 2, 6) <sup>†</sup>	314	238	770.9	1
<b>Anti-HPV 11</b>				
9- to 14-year-old girls (0, 6) <sup>†</sup>	301	258	1388.9	2.39 (2.03, 2.82) <sup>§</sup>
9- to 14-year-old boys (0, 6) <sup>†</sup>	301	264	1423.9	2.45 (2.09, 2.88) <sup>§</sup>
9- to 14-year-old girls and boys (0, 12) <sup>†</sup>	300	257	2941.8	5.07 (4.32, 5.94) <sup>§</sup>
9- to 14-year-old girls (0, 2, 6) <sup>†</sup>	300	254	1306.3	2.25 (1.90, 2.66) <sup>¶</sup>
16- to 26-year-old women (0, 2, 6) <sup>†</sup>	314	238	580.5	1
<b>Anti-HPV 16</b>				
9- to 14-year-old girls (0, 6) <sup>†</sup>	301	272	8004.9	2.54 (2.14, 3.00) <sup>§</sup>
9- to 14-year-old boys (0, 6) <sup>†</sup>	301	273	8474.8	2.69 (2.29, 3.15) <sup>§</sup>
9- to 14-year-old girls and boys (0, 12) <sup>†</sup>	300	264	14329.3	4.54 (3.84, 5.37) <sup>§</sup>
9- to 14-year-old girls (0, 2, 6) <sup>†</sup>	300	269	6996.0	2.22 (1.89, 2.61) <sup>¶</sup>
16- to 26-year-old women (0, 2, 6) <sup>†</sup>	314	249	3154.0	1
<b>Anti-HPV 18</b>				
9- to 14-year-old girls (0, 6) <sup>†</sup>	301	272	1872.8	2.46 (2.05, 2.96) <sup>§</sup>
9- to 14-year-old boys (0, 6) <sup>†</sup>	301	272	1860.9	2.44 (2.04, 2.92) <sup>§</sup>
9- to 14-year-old girls and boys (0, 12) <sup>†</sup>	300	266	2810.4	3.69 (3.06, 4.45) <sup>§</sup>
9- to 14-year-old girls (0, 2, 6) <sup>†</sup>	300	270	2049.3	2.69 (2.24, 3.24) <sup>¶</sup>
16- to 26-year-old women (0, 2, 6) <sup>†</sup>	314	267	761.5	1
<b>Anti-HPV 31</b>				
9- to 14-year-old girls (0, 6) <sup>†</sup>	301	272	1436.3	2.51 (2.10, 3.00) <sup>§</sup>
9- to 14-year-old boys (0, 6) <sup>†</sup>	301	271	1498.2	2.62 (2.20, 3.12) <sup>§</sup>
9- to 14-year-old girls and boys (0, 12) <sup>†</sup>	300	268	2117.5	3.70 (3.08, 4.45) <sup>§</sup>
9- to 14-year-old girls (0, 2, 6) <sup>†</sup>	300	271	1748.3	3.06 (2.54, 3.67) <sup>¶</sup>
16- to 26-year-old women (0, 2, 6) <sup>†</sup>	314	264	572.1	1
<b>Anti-HPV 33</b>				
9- to 14-year-old girls (0, 6) <sup>†</sup>	301	273	1030.0	2.96 (2.50, 3.50) <sup>§</sup>
9- to 14-year-old boys (0, 6) <sup>†</sup>	301	271	1040.0	2.99 (2.55, 3.50) <sup>§</sup>
9- to 14-year-old girls and boys (0, 12) <sup>†</sup>	300	269	2197.5	6.31 (5.36, 7.43) <sup>§</sup>
9- to 14-year-old girls (0, 2, 6) <sup>†</sup>	300	275	796.4	2.29 (1.95, 2.68) <sup>¶</sup>
16- to 26-year-old women (0, 2, 6) <sup>†</sup>	314	279	348.1	1
<b>Anti-HPV 45</b>				
9- to 14-year-old girls (0, 6) <sup>†</sup>	301	274	357.6	1.67 (1.38, 2.03) <sup>§</sup>
9- to 14-year-old boys (0, 6) <sup>†</sup>	301	273	352.3	1.65 (1.37, 1.99) <sup>§</sup>
9- to 14-year-old girls and boys (0, 12) <sup>†</sup>	300	268	417.7	1.96 (1.61, 2.37) <sup>§</sup>
9- to 14-year-old girls (0, 2, 6) <sup>†</sup>	300	275	661.7	3.10 (2.54, 3.77) <sup>¶</sup>
16- to 26-year-old women (0, 2, 6) <sup>†</sup>	314	280	213.6	1
<b>Anti-HPV 52</b>				
9- to 14-year-old girls (0, 6) <sup>†</sup>	301	272	581.1	1.60 (1.36, 1.87) <sup>§</sup>
9- to 14-year-old boys (0, 6) <sup>†</sup>	301	273	640.4	1.76 (1.51, 2.05) <sup>§</sup>
9- to 14-year-old girls and boys (0, 12) <sup>†</sup>	300	268	1123.4	3.08 (2.64, 3.61) <sup>§</sup>
9- to 14-year-old girls (0, 2, 6) <sup>†</sup>	300	275	909.9	2.50 (2.12, 2.95) <sup>¶</sup>
16- to 26-year-old women (0, 2, 6) <sup>†</sup>	314	271	364.2	1
<b>Anti-HPV 58</b>				
9- to 14-year-old girls (0, 6) <sup>†</sup>	301	270	1251.2	2.55 (2.15, 3.01) <sup>§</sup>
9- to 14-year-old boys (0, 6) <sup>†</sup>	301	270	1325.7	2.70 (2.30, 3.16) <sup>§</sup>
9- to 14-year-old girls and boys (0, 12) <sup>†</sup>	300	265	2444.6	4.98 (4.23, 5.86) <sup>§</sup>
9- to 14-year-old girls (0, 2, 6) <sup>†</sup>	300	273	1229.3	2.50 (2.11, 2.97) <sup>¶</sup>

16- to 26-year-old women (0, 2, 6) <sup>†</sup>	314	261	491.1	1
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\*The PPI population consisted of individuals who received all assigned vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the last vaccination dose and blood collection for immunogenicity assessment, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1.

<sup>†</sup>2-dose regimen (0, 6): vaccination at Day 1 and Month 6; 2-dose regimen (0, 12): vaccination at Day 1 and Month 12; 3-dose regimen (0, 2, 6): vaccination at Day 1, Month 2, and Month 6. The data are from Study 8 (NCT01984697).

<sup>‡</sup>mMU=milli-Merck Units

<sup>§</sup>Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

<sup>†</sup>Exploratory analysis; criterion for non-inferiority was not pre-specified

N = Number of individuals randomized to the respective vaccination group who received at least 1 injection

n = Number of individuals contributing to the analysis

CI=Confidence Interval

cLIA=competitive Luminex Immunoassay

GMT=Geometric Mean Titer

#### 14.7 Studies with Menactra and Adacel

In Study 5, the safety and immunogenicity of co-administration of GARDASIL 9 with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] (same visit, injections at separate sites) were evaluated in 1,237 boys and girls 11 through 15 years of age at enrollment.

One group received GARDASIL 9 in one limb and both Menactra and Adacel, as separate injections, in the opposite limb concomitantly on Day 1 (n = 619). The second group received the first dose of GARDASIL 9 on Day 1 in one limb then Menactra and Adacel, as separate injections, at Month 1 in the opposite limb (n = 618). Subjects in both vaccination groups received the second dose of GARDASIL 9 at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines one month post vaccination (one dose for Menactra and Adacel and three doses for GARDASIL 9).

Assessments of post-vaccination immune responses included type-specific antibody GMTs for each of the vaccine HPV types at four weeks following the last dose of GARDASIL 9; GMTs for anti-filamentous hemagglutinin, anti-pertactin, and anti-fimbrial antibodies at four weeks following Adacel; percentage of subjects with anti-tetanus toxin and anti-diphtheria toxin antibody concentrations  $\geq 0.1$  IU/mL at four weeks following Adacel; and percentage of subjects with  $\geq 4$ -fold rise from pre-vaccination baseline in antibody titers against *N. meningitidis* serogroups A, C, Y, and W-135 at four weeks following Menactra. Based on these measures, concomitant administration of GARDASIL 9 with Menactra and Adacel did not interfere with the antibody responses to any of the vaccines when compared with non-concomitant administration of GARDASIL 9 with Menactra and Adacel.

#### 15 REFERENCES

1. Study 1 NCT00543543
2. Study 2 NCT00943722
3. Study 3 NCT01304498
4. Study 4 NCT01047345
5. Study 5 NCT00988884
6. Study 6 NCT01073293
7. Study 7 NCT01651949
8. Study 8 NCT01984697
9. Study A NCT01432574
10. Study B NCT00090285

## 16 HOW SUPPLIED/STORAGE AND HANDLING

GARDASIL 9 is supplied in vials and syringes.

Carton of ten 0.5-mL single-dose vials. NDC 0006-4119-03

Carton of ten 0.5-mL single-dose prefilled Luer Lock syringes with tip caps. NDC 0006-4121-02

Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light.

GARDASIL 9 should be administered as soon as possible after being removed from refrigeration. GARDASIL 9 can be administered provided total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exceed 72 hours. These are not, however, recommendations for storage.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform the patient, parent, or guardian:

- Vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL 9 should continue to undergo cervical cancer screening per standard of care.
  - Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care provider.
  - GARDASIL 9 has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity.
  - Since syncope has been reported following HPV vaccination sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended.
  - Vaccine information is required to be given with each vaccination to the patient, parent, or guardian.
  - Provide information regarding benefits and risks associated with vaccination.
  - Safety and effectiveness of GARDASIL 9 have not been established in pregnant women. A pregnancy registry is available. Women exposed to GARDASIL 9 around the time of conception or during pregnancy are encouraged to register by calling 1-800-986-8999. *[See Use in Specific Populations (8.1).]*
  - It is important to complete the full vaccination series unless contraindicated.
  - Report any adverse reactions to their health care provider.
- 

 Manuf. and Dist. by: Merck Sharp & Dohme Corp., a subsidiary of  
**MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

For patent information: [www.merck.com/product/patent/home.html](http://www.merck.com/product/patent/home.html)

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uspi-v503-i-2006r011

# **EXHIBIT 260**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Menactra® safely and effectively. See full prescribing information for Menactra vaccine.

**Menactra®, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine Solution for Intramuscular Injection**

**Initial U.S. Approval: 2005**

-----**RECENT MAJOR CHANGES**-----  
**Warnings and Precautions, Altered Immunocompetence (5.3) 4/2018**

-----**INDICATIONS AND USAGE**-----  
Menactra is indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135. Menactra is approved for use in individuals 9 months through 55 years of age. Menactra does not prevent *N meningitidis* serogroup B disease. (1)

-----**DOSAGE AND ADMINISTRATION**-----  
A 0.5 mL dose for intramuscular injection. (2)

### Primary Vaccination:

- Children 9 through 23 months of age: Two doses, three months apart.
- Individuals 2 through 55 years of age: A single dose.

### Booster Vaccination:

- A single booster dose may be given to individuals 15 through 55 years of age at continued risk for meningococcal disease, if at least 4 years have elapsed since the prior dose.

-----**DOSAGE FORMS AND STRENGTHS**-----  
Solution supplied in 0.5 mL single-dose vials (3)

-----**CONTRAINDICATIONS**-----  
• Severe allergic reaction (eg, anaphylaxis) after a previous dose of a meningococcal capsular polysaccharide-, diphtheria toxoid- or CRM<sub>197</sub>-containing vaccine, or to any component of Menactra. (4)

-----**WARNINGS AND PRECAUTIONS**-----  
• Persons previously diagnosed with Guillain-Barré syndrome (GBS) may be at increased risk of GBS following receipt of Menactra. The decision to give Menactra should take into account the potential benefits and risks. (5.1)

-----**ADVERSE REACTIONS**-----  
• Common (≥10%) solicited adverse events in infants and toddlers 9 and 12 months of age were injection site tenderness, erythema, and swelling; irritability, abnormal crying, drowsiness, appetite loss, vomiting, and fever. (6)  
• Common (≥10%) solicited adverse events in individuals 2 through 55 years of age who received a single dose were injection site pain, redness, induration, and swelling; anorexia and diarrhea. Other common solicited adverse events were irritability and drowsiness (2-10 years of age), headache, fatigue, malaise, and arthralgia (11-55 years of age). (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or <http://vaers.hhs.gov>.**

-----**DRUG INTERACTIONS**-----  
• When Menactra and DAPTACEL® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) are to be administered to children 4 through 6 years of age, preference should be given to simultaneous administration of the 2 vaccines or administration of Menactra prior to DAPTACEL. Administration of Menactra one month after DAPTACEL has been shown to reduce meningococcal antibody responses to Menactra. (7.1)  
• Pneumococcal antibody responses to some serotypes in Prevnar (PCV7) were decreased following co-administration of Menactra and PCV7. (7.1)

-----**USE IN SPECIFIC POPULATIONS**-----  
• Safety and effectiveness of Menactra have not been established in children younger than 9 months of age, pregnant women, nursing mothers, and adults older than 55 years of age. (8.1, 8.2, 8.4, 8.5)  
• A pregnancy registry is available. Contact Sanofi Pasteur Inc. at 1-800-822-2463. (8.1)

See **17 PATIENT\_COUNSELING\_INFORMATION**.  
**Revised: April 2018**

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## FULL PRESCRIBING INFORMATION:

### 1 INDICATIONS AND USAGE

Menactra®, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine, is indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135. Menactra is approved for use in individuals 9 months through 55 years of age. Menactra does not prevent *N meningitidis* serogroup B disease.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Preparation for Administration

Menactra is a clear to slightly turbid solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If any of these conditions exist, the vaccine should not be administered.

Withdraw the 0.5 mL dose of vaccine from the single-dose vial using a sterile needle and syringe.

#### 2.2 Dose and Schedule

Menactra is administered as a 0.5 mL dose by intramuscular injection. Do not administer this product intravenously or subcutaneously.

##### *Primary Vaccination:*

- In children 9 through 23 months of age, Menactra is given as a 2-dose series three months apart.

- Individuals 2 through 55 years of age, Menactra is given as a single dose.

#### **Booster Vaccination:**

- A single booster dose may be given to individuals 15 through 55 years of age at continued risk for meningococcal disease, if at least 4 years have elapsed since the prior dose.

### **3 DOSAGE FORMS AND STRENGTHS**

Menactra is a solution supplied in 0.5 mL single-dose vials. [See *Description (11)* for a complete listing of ingredients.]

### **4 CONTRAINDICATIONS**

Severe allergic reaction (eg, anaphylaxis) after a previous dose of a meningococcal capsular polysaccharide-, diphtheria toxoid- or CRM<sub>197</sub>-containing vaccine, or to any component of Menactra [see *Description (11)*].

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Guillain-Barré Syndrome**

Persons previously diagnosed with Guillain-Barré syndrome (GBS) may be at increased risk of GBS following receipt of Menactra. The decision to give Menactra should take into account the potential benefits and risks.

GBS has been reported in temporal relationship following administration of Menactra (1) (2). The risk of GBS following Menactra vaccination was evaluated in a post-marketing retrospective cohort study [see *Post-Marketing Experience* (6.2)].

## 5.2 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

## 5.3 Altered Immunocompetence

- *Reduced Immune Response*

Some individuals with altered immunocompetence, including some individuals receiving immunosuppressant therapy, may have reduced immune responses to Menactra.

- *Complement Deficiency*

Persons with certain complement deficiencies and persons receiving treatment that inhibits terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *N meningitidis*, including invasive disease caused by serogroups A, C, Y and W-135, even if they develop antibodies following vaccination with Menactra. [See *Clinical Pharmacology* (12).]

## 5.4 Limitations of Vaccine Effectiveness

Menactra may not protect all recipients.

## 5.5 Syncope

Syncope (fainting) has been reported following vaccination with Menactra. Procedures should be in place to prevent falling injury and manage syncopal reactions.

# 6 ADVERSE REACTIONS

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

### *Children 9 Through 12 Months of Age*

The safety of Menactra was evaluated in four clinical studies that enrolled 3721 participants who received Menactra at 9 and 12 months of age. At 12 months of age these children also received one or more other recommended vaccines [Measles, Mumps, Rubella and Varicella Virus Vaccine Live (MMRV) or Measles, Mumps, and Rubella Virus Vaccine (MMR) and Varicella Virus Vaccine Live (V) each manufactured by Merck & Co., Inc., Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein) manufactured by Wyeth Pharmaceuticals Inc. (PCV7), Hepatitis A Vaccine manufactured by Merck & Co., Inc. (HepA). A control group of 997 children

was enrolled at 12 months of age and received two or more childhood vaccines [MMRV (or MMR+V), PCV7, HepA] at 12 months of age [see *Concomitant Vaccine Administration (14.3)*]. Three percent of individuals received MMR and V, instead of MMRV, at 12 months of age.

The primary safety study was a controlled trial that enrolled 1256 children who received Menactra at 9 and 12 months of age. At 12 months of age these children received MMRV (or MMR+V), PCV7 and HepA. A control group of 522 children received MMRV, PCV7 and HepA. Of the 1778 children, 78% of participants (Menactra, N=1056; control group, N=322) were enrolled at United States (US) sites and 22% at a Chilean site. (Menactra, N=200; control group, N=200).

#### ***Individuals 2 Through 55 Years of Age***

The safety of Menactra was evaluated in eight clinical studies that enrolled 10,057 participants aged 2-55 years who received Menactra and 5,266 participants who received Menomune® – A/C/Y/W-135, Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined.

There were no substantive differences in demographic characteristics between the vaccine groups. Among Menactra recipients 2-55 years of age 24.0%, 16.2%, 40.4% and 19.4% were in the 2-10, 11-14, 15-25 and 26-55-year age groups, respectively. Among Menomune – A/C/Y/W-135 recipients 2-55 years of age 42.3%, 9.3%, 30.0% and 18.5% were in the 2-10, 11-14, 15-25 and 26-55-year age groups, respectively. The three primary safety studies were randomized, active-controlled trials that enrolled participants 2-10 years of age (Menactra, N=1713; Menomune – A/C/Y/W-135, N=1519), 11-18 years of age (Menactra, N=2270; Menomune – A/C/Y/W-135, N=972) and 18-55 years of age (Menactra, N=1384; Menomune – A/C/Y/W-135, N=1170), respectively. Of the 3232 children 2-10 years of age, 68% of participants (Menactra, N=1164;

Menomune – A/C/Y/W-135, N=1031) were enrolled at US sites and 32% (Menactra, N=549; Menomune – A/C/Y/W-135, N=488) of participants at a Chilean site. The median ages in the Chilean and US subpopulations were 5 and 6 years, respectively. All adolescents and adults were enrolled at US sites. As the route of administration differed for the two vaccines (Menactra given intramuscularly, Menomune – A/C/Y/W-135 given subcutaneously), study personnel collecting the safety data differed from personnel administering the vaccine.

### ***Booster Vaccination Study***

In an open-label trial conducted in the US, 834 individuals were enrolled to receive a single dose of Menactra 4-6 years after a prior dose. The median age of participants was 17.1 years at the time of the booster dose.

### ***Safety Evaluation***

Participants were monitored after each vaccination for 20 or 30 minutes for immediate reactions, depending on the study. Solicited injection site and systemic reactions were recorded in a diary card for 7 consecutive days after each vaccination. Participants were monitored for 28 days (30 days for infants and toddlers) for unsolicited adverse events and for 6 months post-vaccination for visits to an emergency room, unexpected visits to an office physician, and serious adverse events. Unsolicited adverse event information was obtained either by telephone interview or at an interim clinic visit. Information regarding adverse events that occurred in the 6-month post-vaccination time period was obtained via a scripted telephone interview.



***Serious Adverse Events in All Safety Studies***

Serious adverse events (SAEs) were reported during a 6-month time period following vaccinations in individuals 9 months through 55 years of age. In children who received Menactra at 9 months and at 12 months of age, SAEs occurred at a rate of 2.0% - 2.5%. In participants who received one or more childhood vaccine(s) (without co-administration of Menactra) at 12 months of age, SAEs occurred at a rate of 1.6% - 3.6%, depending on the number and type of vaccines received. In children 2-10 years of age, SAEs occurred at a rate of 0.6% following Menactra and at a rate of 0.7% following Menomune – A/C/Y/W-135. In adolescents 11 through 18 years of age and adults 18 years through 55 years of age, SAEs occurred at a rate of 1.0% following Menactra and at a rate of 1.3% following Menomune – A/C/Y/W-135. In adolescents and adults, SAEs occurred at a rate of 1.3% following booster vaccination with Menactra.

***Solicited Adverse Events in the Primary Safety Studies***

The most frequently reported solicited injection site and systemic adverse reactions within 7 days following vaccination in children 9 months and 12 months of age (Table 1) were injection site tenderness and irritability.

The most frequently reported solicited injection site and systemic adverse reactions in US children aged 2-10 years of age (Table 2) were injection site pain and irritability. Diarrhea, drowsiness, and anorexia were also common.

The most commonly reported solicited injection site and systemic adverse reactions in adolescents, ages 11-18 years (Table 3), and adults, ages 18-55 years (Table 4), after a single dose

1 were injection site pain, headache and fatigue. Except for redness in adults, injection site reactions  
2 were more frequently reported after Menactra vaccination than after Menomune – A/C/Y/W-135  
3 vaccination.  
4

**1 Table 1: Percentage of US Participants Reporting Solicited Adverse Reactions Within 7**

**2 Days Following Vaccine Administration at 9 Months and 12 Months of Age**

	Menactra at 9 months of age  N <sup>d</sup> =998 - 1002			Menactra + PCV7 <sup>a</sup> + MMRV <sup>b</sup> + HepA <sup>c</sup> at 12 months of age  N <sup>d</sup> =898 - 908			PCV7 <sup>a</sup> + MMRV <sup>b</sup> + HepA <sup>c</sup> at 12 months of age  N <sup>d</sup> =302 - 307		
Reaction	Any	Grade 2	Grade 3	Any	Grade 2	Grade 3	Any	Grade 2	Grade 3
<b>Local/Injection Site</b>									
<b>Tenderness<sup>e</sup></b>									
Menactra Site	37.4	4.3	0.6	48.5	7.5	1.3	-	-	-
PCV7 Site	-	-	-	45.6	9.4	1.6	45.7	8.3	0.3
MMRV Site	-	-	-	38.9	7.1	1.0	43.0	5.2	0.0
HepA Site	-	-	-	43.4	8.7	1.4	40.9	4.6	0.3
<b>Erythema<sup>f</sup></b>									
Menactra Site	30.2	2.5	0.3	30.1	1.3	0.1	-	-	-
PCV7 Site	-	-	-	29.4	2.6	0.2	32.6	3.0	0.7
MMRV Site	-	-	-	22.5	0.9	0.3	33.2	5.9	0.0
HepA Site	-	-	-	25.1	1.1	0.0	26.6	0.7	0.0
<b>Swelling<sup>f</sup></b>									
Menactra Site	16.8	0.9	0.2	16.2	0.9	0.1	-	-	-
PCV7 Site	-	-	-	19.5	1.3	0.4	16.6	1.3	0.7
MMRV Site	-	-	-	12.1	0.4	0.1	14.1	0.3	0.0
HepA Site	-	-	-	16.4	0.7	0.2	13.5	0.0	0.3
<b>Systemic</b>									
Irritability <sup>g</sup>	56.8	23.1	2.9	62.1	25.7	3.7	64.8	28.7	4.2
Abnormal crying <sup>h</sup>	33.3	8.3	2.0	40.0	11.5	2.4	39.4	10.1	0.7
Drowsiness <sup>i</sup>	30.2	3.5	0.7	39.8	5.3	1.1	39.1	5.2	0.7
Appetite loss <sup>j</sup>	30.2	7.1	1.2	35.7	7.6	2.6	31.9	6.5	0.7
Vomiting <sup>k</sup>	14.1	4.6	0.3	11.0	4.4	0.2	9.8	2.0	0.0
Fever <sup>l</sup>	12.2	4.5	1.1	24.5	11.9	2.2	21.8	7.3	2.6

3 <sup>a</sup> PCV7 (Prevnar<sup>®</sup>) = Pneumococcal 7-valent Conjugate Vaccine

4 <sup>b</sup> MMRV (ProQuad<sup>®</sup>) = Measles, Mumps, Rubella and Varicella Virus Vaccine Live

<sup>c</sup> HepA (VAQTA®) = Hepatitis A Vaccine, Inactivated

<sup>d</sup> N = The number of participants with available data.

<sup>e</sup> Grade 2: cries and protests when injection site is touched, Grade 3: cries when injected limb is moved, or the movement of the injected limb is reduced.

<sup>f</sup> Grade 2:  $\geq 1.0$  inches to  $< 2.0$  inches, Grade 3:  $\geq 2.0$  inches.

<sup>g</sup> Grade 2: requires increased attention, Grade 3: inconsolable.

<sup>h</sup> Grade 2: 1 to 3 hours, Grade 3:  $> 3$  hours.

<sup>i</sup> Grade 2: not interested in surroundings or did not wake up for a feed/meal, Grade 3: sleeping most of the time or difficult to wake up.

<sup>j</sup> Grade 2: missed 1 or 2 feeds/meals completely, Grade 3: refuses  $\geq 3$  feeds/meals or refuses most feeds/meals.

<sup>k</sup> Grade 2: 2 to 5 episodes per 24 hours, Grade 3:  $\geq 6$  episodes per 24 hours or requiring parenteral hydration.

<sup>l</sup> Grade 2:  $> 38.5^{\circ}\text{C}$  to  $\leq 39.5^{\circ}\text{C}$ , Grade 3:  $> 39.5^{\circ}\text{C}$ .

**Table 2: Percentage of US Participants 2 Years Through 10 Years of Age Reporting**

**Solicited Adverse Reactions Within 7 Days Following Vaccine Administration**

	Menactra			Menomune – A/C/Y/W-135		
	N <sup>a</sup> =1156 - 1157			N <sup>a</sup> =1027		
Reaction	Any	Grade 2	Grade 3	Any	Grade 2	Grade 3
<b>Local/Injection Site</b>						
Pain <sup>b</sup>	45.0	4.9	0.3	26.1	2.5	0.0
Redness <sup>c</sup>	21.8	4.6	3.9	7.9	0.5	0.0
Induration <sup>c</sup>	18.9	3.4	1.4	4.2	0.6	0.0
Swelling <sup>c</sup>	17.4	3.9	1.9	2.8	0.3	0.0
<b>Systemic</b>						
Irritability <sup>d</sup>	12.4	3.0	0.3	12.2	2.6	0.6
Diarrhea <sup>e</sup>	11.1	2.1	0.2	11.8	2.5	0.3
Drowsiness <sup>f</sup>	10.8	2.7	0.3	11.2	2.5	0.5
Anorexia <sup>g</sup>	8.2	1.7	0.4	8.7	1.3	0.8
Arthralgia <sup>h</sup>	6.8	0.5	0.2	5.3	0.7	0.0
Fever <sup>i</sup>	5.2	1.7	0.3	5.2	1.7	0.2
Rash <sup>j</sup>	3.4	-	-	3.0	-	-
Vomiting <sup>k</sup>	3.0	0.7	0.3	2.7	0.7	0.6
Seizure <sup>j</sup>	0.0	-	-	0.0	-	-

<sup>a</sup> N = The total number of participants reporting at least one solicited reaction. The median age of participants was 6 years in both vaccine groups.

<sup>b</sup> Grade 2: interferes with normal activities, Grade 3: disabling, unwilling to move arm.

<sup>c</sup> Grade 2: 1.0-2.0 inches, Grade 3: >2.0 inches.

<sup>d</sup> Grade 2: 1-3 hours duration, Grade 3: >3 hours duration.

<sup>e</sup> Grade 2: 3-4 episodes, Grade 3: ≥5 episodes.

<sup>f</sup> Grade 2: interferes with normal activities, Grade 3: disabling, unwilling to engage in play or interact with others.

<sup>g</sup> Grade 2: skipped 2 meals, Grade 3: skipped ≥3 meals.

<sup>h</sup> Grade 2: decreased range of motion due to pain or discomfort, Grade 3: unable to move major joints due to pain.

<sup>i</sup> Oral equivalent temperature; Grade 2: 38.4°C to 39.4°C, Grade 3:  $\geq 39.5^\circ\text{C}$ .

<sup>j</sup> These solicited adverse events were reported as present or absent only.

<sup>k</sup> Grade 2: 2 episodes, Grade 3:  $\geq 3$  episodes.

Note: During the study Grade 1, Grade 2, and Grade 3 were collected as Mild, Moderate, and Severe respectively.



**Table 3: Percentage of Participants 11 Years Through 18 Years of Age Reporting Solicited**

**Adverse Reactions Within 7 Days Following Vaccine Administration With a Single Dose**

	Menactra N <sup>a</sup> =2264 - 2265			Menomune – A/C/Y/W-135 N <sup>a</sup> =970		
Reaction	Any	Grade 2	Grade 3	Any	Grade 2	Grade 3
<b>Local/Injection Site</b>						
Pain <sup>b</sup>	59.2 <sup>c</sup>	12.8 <sup>c</sup>	0.3	28.7	2.6	0.0
Induration <sup>d</sup>	15.7 <sup>c</sup>	2.5 <sup>c</sup>	0.3	5.2	0.5	0.0
Redness <sup>d</sup>	10.9 <sup>c</sup>	1.6 <sup>c</sup>	0.6 <sup>c</sup>	5.7	0.4	0.0
Swelling <sup>d</sup>	10.8 <sup>c</sup>	1.9 <sup>c</sup>	0.5 <sup>c</sup>	3.6	0.3	0.0
<b>Systemic</b>						
Headache <sup>e</sup>	35.6 <sup>c</sup>	9.6 <sup>c</sup>	1.1	29.3	6.5	0.4
Fatigue <sup>e</sup>	30.0 <sup>c</sup>	7.5	1.1 <sup>c</sup>	25.1	6.2	0.2
Malaise <sup>e</sup>	21.9 <sup>c</sup>	5.8 <sup>c</sup>	1.1	16.8	3.4	0.4
Arthralgia <sup>e</sup>	17.4 <sup>c</sup>	3.6 <sup>c</sup>	0.4	10.2	2.1	0.1
Diarrhea <sup>f</sup>	12.0	1.6	0.3	10.2	1.3	0.0
Anorexia <sup>g</sup>	10.7 <sup>c</sup>	2.0	0.3	7.7	1.1	0.2
Chills <sup>e</sup>	7.0 <sup>c</sup>	1.7 <sup>c</sup>	0.2	3.5	0.4	0.1
Fever <sup>h</sup>	5.1 <sup>c</sup>	0.6	0.0	3.0	0.3	0.1
Vomiting <sup>i</sup>	1.9	0.4	0.3	1.4	0.5	0.3
Rash <sup>j</sup>	1.6	-	-	1.4	-	-
Seizure <sup>j</sup>	0.0	-	-	0.0	-	-

<sup>a</sup> N = The number of participants with available data.

<sup>b</sup> Grade 2: interferes with or limits usual arm movement, Grade 3: disabling, unable to move arm.

<sup>c</sup> Denotes  $p < 0.05$  level of significance. The  $p$ -values were calculated for each category and severity using Chi Square test.

<sup>d</sup> Grade 2: 1.0-2.0 inches, Grade 3: >2.0 inches.

<sup>e</sup> Grade 2: interferes with normal activities, Grade 3: requiring bed rest.

<sup>f</sup> Grade 2: 3-4 episodes, Grade 3:  $\geq 5$  episodes.

- 1 <sup>g</sup> Grade 2: skipped 2 meals, Grade 3: skipped  $\geq 3$  meals.
- 2 <sup>h</sup> Oral equivalent temperature; Grade 2: 38.5°C to 39.4°C, Grade 3:  $\geq 39.5^\circ\text{C}$ .
- 3 <sup>i</sup> Grade 2: 2 episodes, Grade 3:  $\geq 3$  episodes.
- 4 <sup>j</sup> These solicited adverse events were reported as present or absent only.
- 5 Note: During the study Grade 1, Grade 2, and Grade 3 were collected as Mild, Moderate, and Severe respectively.
- 6
- 7

**1 Table 4: Percentage of Participants 18 Years Through 55 Years of Age Reporting Solicited**

**2 Adverse Reactions Within 7 Days Following Vaccine Administration With a Single Dose**

	Menactra			Menomune – A/C/Y/W-135		
	N <sup>a</sup> =1371			N <sup>a</sup> =1159		
Reaction	Any	Grade 2	Grade 3	Any	Grade 2	Grade 3
<b>Local/Injection Site</b>						
Pain <sup>b</sup>	53.9 <sup>c</sup>	11.3 <sup>c</sup>	0.2	48.1	3.3	0.1
Induration <sup>d</sup>	17.1 <sup>c</sup>	3.4 <sup>c</sup>	0.7 <sup>c</sup>	11.0	1.0	0.0
Redness <sup>d</sup>	14.4	2.9	1.1 <sup>c</sup>	16.0	1.9	0.1
Swelling <sup>d</sup>	12.6 <sup>c</sup>	2.3 <sup>c</sup>	0.9 <sup>c</sup>	7.6	0.7	0.0
<b>Systemic</b>						
Headache <sup>e</sup>	41.4	10.1	1.2	41.8	8.9	0.9
Fatigue <sup>e</sup>	34.7	8.3	0.9	32.3	6.6	0.4
Malaise <sup>e</sup>	23.6	6.6 <sup>c</sup>	1.1	22.3	4.7	0.9
Arthralgia <sup>e</sup>	19.8 <sup>c</sup>	4.7 <sup>c</sup>	0.3	16.0	2.6	0.1
Diarrhea <sup>f</sup>	16.0	2.6	0.4	14.0	2.9	0.3
Anorexia <sup>g</sup>	11.8	2.3	0.4	9.9	1.6	0.4
Chills <sup>e</sup>	9.7 <sup>c</sup>	2.1 <sup>c</sup>	0.6 <sup>c</sup>	5.6	1.0	0.0
Vomiting <sup>h</sup>	2.3	0.4	0.2	1.5	0.2	0.4
Fever <sup>i</sup>	1.5 <sup>c</sup>	0.3	0.0	0.5	0.1	0.0
Rash <sup>j</sup>	1.4	-	-	0.8	-	-
Seizure <sup>j</sup>	0.0	-	-	0.0	-	-

3 <sup>a</sup>N = The number of participants with available data.

4 <sup>b</sup>Grade 2: interferes with or limits usual arm movement, Grade 3: disabling, unable to move arm.

5 <sup>c</sup>Denotes  $p < 0.05$  level of significance. The  $p$ -values were calculated for each category and severity using Chi Square  
6 test.

7 <sup>d</sup>Grade 2: 1.0-2.0 inches, Grade 3: >2.0 inches.

8 <sup>e</sup>Grade 2: interferes with normal activities, Grade 3: requiring bed rest.

9 <sup>f</sup>Grade 2: 3-4 episodes, Grade 3:  $\geq 5$  episodes.

<sup>g</sup> Grade 2: skipped 2 meals, Grade 3: skipped  $\geq 3$  meals.

<sup>h</sup> Grade 2: 2 episodes, Grade 3:  $\geq 3$  episodes.

<sup>i</sup> Oral equivalent temperature; Grade 2: 39.0°C to 39.9°C, Grade 3:  $\geq 40.0^\circ\text{C}$ .

<sup>j</sup> These solicited adverse events were reported as present or absent only.

Note: During the study Grade 1, Grade 2, and Grade 3 were collected as Mild, Moderate, and Severe respectively.

### ***Solicited Adverse Events in a Booster Vaccination Study***

For a description of the study design and number of participants, [see *Clinical Trials Experience, Booster Vaccination Study (6.1)*]. The most common solicited injection site and systemic reactions within 7 days of vaccination were pain (60.2%) and myalgia (42.8%), respectively.

Overall rates of solicited injection site reactions and solicited systemic reactions were similar to those observed in adolescents and adults after a single Menactra dose. The majority of solicited reactions were Grade 1 or 2 and resolved within 3 days.

### ***Adverse Events in Concomitant Vaccine Studies***

#### **Solicited Injection Site and Systemic Reactions when Given with Routine Pediatric Vaccines**

For a description of the study design and number of participants, [see *Clinical Trials Experience (6.1), Concomitant Vaccine Administration (14.3)*]. In the primary safety study, 1378 US children were enrolled to receive Menactra alone at 9 months of age and Menactra plus one or more other routinely administered vaccines (MMRV, PCV7 and HepA) at 12 months of age (N=961).

Another group of children received two or more routinely administered vaccines (MMRV, PCV7 and HepA) (control group, n=321) at 12 months of age. The frequency of occurrence of solicited adverse events is presented in [Table 1](#). Participants who received Menactra and the concomitant

1 vaccines at 12 months of age described above reported similar frequencies of tenderness, redness  
2 and swelling at the Menactra injection site and at the concomitant vaccine injection sites.  
3 Tenderness was the most frequent injection site reaction (48%, 39%, 46% and 43% at the  
4 Menactra, MMRV, PCV7 and HepA sites, respectively). Irritability was the most frequent  
5 systemic reaction, reported in 62% of recipients of Menactra plus concomitant vaccines, and 65%  
6 of the control group. [See *Concomitant Vaccine Administration* (14.3).]  
7

8 In a randomized, parallel group, US multi-center clinical trial conducted in children 4 through 6  
9 years of age, Menactra was administered as follows: 30 days after concomitant DAPTACEL<sup>®</sup>,  
10 Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, (DTaP),  
11 manufactured by Sanofi Pasteur Limited + IPOL<sup>®</sup>, Poliovirus Vaccine Inactivated, (IPV),  
12 manufactured by Sanofi Pasteur SA [Group A]; concomitantly with DAPTACEL followed 30  
13 days later by IPV [Group B]; concomitantly with IPV followed 30 days later by DAPTACEL  
14 [Group C]. Solicited injection site and systemic reactions were recorded in a diary card for 7  
15 consecutive days after each vaccination. For all study groups, the most frequently reported  
16 solicited local reaction at the Menactra site was pain: 52.2%, 60.9% and 56.0% of participants in  
17 Groups A, B and C, respectively. For all study groups, the most frequently reported systemic  
18 reaction following the administration of Menactra alone or with the respective concomitant  
19 vaccines was myalgia: 24.2%, 37.3% and 26.7% of participants in Groups A, B and C,  
20 respectively. Fever >39.5°C occurred at <1.0% in all groups. [See *Concomitant Vaccine*  
21 *Administration* (14.3).]  
22

**Solicited Injection Site and Systemic Reactions when Given with Tetanus and Diphtheria Toxoid Adsorbed Vaccine**

In a clinical study, rates of local and systemic reactions after Menactra and Tetanus and Diphtheria Toxoid Adsorbed (Td) vaccine manufactured by Sanofi Pasteur Inc. were compared [see *Drug Interactions* (7), and *Concomitant Vaccine Administration* (14.3) for study description]. Injection site pain was reported more frequently after Td vaccination than after Menactra vaccination (71% versus 53%). The overall rate of systemic adverse events was higher when Menactra and Td vaccines were given concomitantly than when Menactra was administered 28 days after Td vaccine (59% versus 36%). In both groups, the most common reactions were headache (Menactra + Td vaccine, 36%; Td vaccine + Placebo, 34%; Menactra alone, 22%) and fatigue (Menactra + Td vaccine, 32%; Td vaccine + Placebo, 29%; Menactra alone, 17%). Fever  $\geq 40.0^{\circ}\text{C}$  occurred at  $\leq 0.5\%$  in all groups.

**Solicited Injection Site and Systemic Reactions when Given with Typhoid Vi Polysaccharide Vaccine**

In a clinical study, rates of local and systemic reactions after Menactra and Typhim Vi® [Typhoid Vi Polysaccharide Vaccine] (Typhoid), produced by Sanofi Pasteur SA were compared [see *Drug Interactions* (7) and *Concomitant Vaccine Administration* (14.3)] for a description of the concomitantly administered vaccine, study design and number of participants. More participants experienced pain after Typhoid vaccination than after Menactra vaccination (Typhoid + Placebo, 76% versus Menactra + Typhoid, 47%). The majority (70%-77%) of injection site solicited reactions for both groups at either injection site were reported as Grade 1 and resolved within 3 days post-vaccination. In both groups, the most common systemic reaction was headache (Menactra +



Typhoid, 41%; Typhoid + Placebo, 42%; Menactra alone, 33%) and fatigue (Menactra + Typhoid, 38%; Typhoid + Placebo, 35%; Menactra alone, 27%). Fever  $\geq 40.0^{\circ}\text{C}$  and seizures were not reported in either group.

## 6.2 Post-Marketing Experience

In addition to reports in clinical trials, worldwide voluntary adverse events reports received since market introduction of Menactra are listed below. This list includes serious events and/or events which were included based on severity, frequency of reporting or a plausible causal connection to Menactra. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccination.

- *Blood and Lymphatic System Disorders*

Lymphadenopathy

- *Immune System Disorders*

Hypersensitivity reactions such as anaphylaxis/anaphylactic reaction, wheezing, difficulty breathing, upper airway swelling, urticaria, erythema, pruritus, hypotension

- *Nervous System Disorders*

Guillain-Barré syndrome, paraesthesia, vasovagal syncope, dizziness, convulsion, facial palsy, acute disseminated encephalomyelitis, transverse myelitis

- *Musculoskeletal and Connective Tissue Disorders*

Myalgia

- *General Disorders and Administrative Site Conditions*

Large injection site reactions, extensive swelling of the injected limb (may be associated with erythema, warmth, tenderness or pain at the injection site).

### ***Post-marketing Safety Study***

The risk of GBS following receipt of Menactra was evaluated in a US retrospective cohort study using healthcare claims data from 9,578,688 individuals 11 through 18 years of age, of whom 1,431,906 (15%) received Menactra. Of 72 medical chart-confirmed GBS cases, none had received Menactra within 42 days prior to symptom onset. An additional 129 potential cases of GBS could not be confirmed or excluded due to absent or insufficient medical chart information. In an analysis that took into account the missing data, estimates of the attributable risk of GBS ranged from 0 to 5 additional cases of GBS per 1,000,000 vaccinees within the 6-week period following vaccination.

## **7 DRUG INTERACTIONS**

### **7.1 Concomitant Administration with Other Vaccines**

Menactra vaccine was concomitantly administered with Typhim Vi® [Typhoid Vi Polysaccharide Vaccine] (Typhoid) and Tetanus and Diphtheria Toxoids Adsorbed, For Adult Use (Td) vaccine, in individuals 18 through 55 and 11 through 17 years of age, respectively. In children 4 through 6 years of age, Menactra was co-administered with DAPTACEL, and in children younger than 2

years of age, Menactra was co-administered with one or more of the following vaccines: PCV7, MMR, V, MMRV, or HepA [see *Clinical Studies* (14) and *Adverse Reactions* (6)].

When Menactra and DAPTACEL are to be administered to children 4 through 6 years of age, preference should be given to simultaneous administration of the 2 vaccines or administration of Menactra prior to DAPTACEL. Administration of Menactra one month after DAPTACEL has been shown to reduce meningococcal antibody responses to Menactra. Data are not available to evaluate the immune response to Menactra administered to younger children following DAPTACEL or to Menactra administered to persons <11 years of age following other diphtheria toxoid-containing vaccines [see *Clinical Studies* (14.3)].

Pneumococcal antibody responses to some serotypes in PCV7 were decreased following co-administration of Menactra and PCV7 [see *Concomitant Vaccine Administration* (14.3)].

Do not mix Menactra with other vaccines in the same syringe. When Menactra is administered concomitantly with other injectable vaccines, the vaccines should be administered with different syringes and given at separate injection sites.

## 7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Menactra during pregnancy. To enroll in or obtain information about the registry, call Sanofi Pasteur at 1-800-822-2463.

#### Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are no adequate and well-controlled studies of Menactra administration in pregnant women in the US. Available data suggest that rates of major birth defects and miscarriage in women who received Menactra 30 days prior to pregnancy or during pregnancy are consistent with estimated background rates.

A developmental toxicity study was performed in female mice given 0.1 mL (in divided doses) of Menactra prior to mating and during gestation (a single human dose is 0.5 mL). The study revealed no evidence of harm to the fetus due to Menactra [see *Animal Data* (8.1)].

#### Data

##### *Human Data*

A pregnancy registry spanning 11 years (2005-2016) included 222 reports of exposure to Menactra from 30 days before or at any time during pregnancy. Of these reports, 87 had known

pregnancy outcomes available and were enrolled in the pregnancy registry prior to the outcomes being known. Outcomes among these prospectively followed pregnancies included 2 major birth defects and 6 miscarriages.

#### *Animal Data*

A developmental toxicity study was performed in female mice. The animals were administered 0.1 mL of Menactra (in divided doses) at each of the following time points: 14 days prior to mating, and on Days 6 and 18 of gestation (a single human dose is 0.5 mL). There were no vaccine-related fetal malformations or variations, and no adverse effects on pre-weaning development observed in the study.

## **8.2 Lactation**

### Risk Summary

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Menactra and any potential adverse effects on the breastfed child from Menactra. Data are not available to assess the effects of Menactra on the breastfed infant or on milk production/excretion.

## **8.4 Pediatric Use**

Menactra is not approved for use in infants under 9 months of age. Available data show that infants administered three doses of Menactra (at 2, 4, and 6 months of age) had diminished responses to each meningococcal vaccine serogroup compared to older children given two doses at 9 and 12 months of age.

## 8.5 Geriatric Use

Safety and effectiveness of Menactra in adults older than 55 years of age have not been established.

## 11 DESCRIPTION

Menactra is a sterile, intramuscularly administered vaccine that contains *N meningitidis* serogroup A, C, Y and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxoid protein. *N meningitidis* A, C, Y and W-135 strains are cultured on Mueller Hinton agar (3) and grown in Watson Scherp (4) media containing casamino acid. The polysaccharides are extracted from the *N meningitidis* cells and purified by centrifugation, detergent precipitation, alcohol precipitation, solvent extraction and diafiltration. To prepare the polysaccharides for conjugation, they are depolymerized, derivatized, and purified by diafiltration. Diphtheria toxin is derived from *Corynebacterium diphtheriae* grown in modified culture medium containing hydrolyzed casein (5) and is detoxified using formaldehyde. The diphtheria toxoid protein is purified by ammonium sulfate fractionation and diafiltration. The derivatized polysaccharides are covalently linked to diphtheria toxoid and purified by serial diafiltration. The four meningococcal components, present as individual serogroup-specific glycoconjugates, compose the final formulated vaccine. No preservative or adjuvant is added during manufacture. Each 0.5 mL dose may contain residual amounts of formaldehyde of less than 2.66 mcg (0.000532%), by calculation. Potency of Menactra is determined by quantifying the amount of each polysaccharide antigen that is conjugated to diphtheria toxoid protein and the amount of unconjugated polysaccharide present.

Menactra is manufactured as a sterile, clear to slightly turbid liquid. Each 0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 mcg each of meningococcal A, C, Y and W-135 polysaccharides conjugated to approximately 48 mcg of diphtheria toxoid protein carrier.

The vial stopper is not made with natural rubber latex.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The presence of bactericidal anti-capsular meningococcal antibodies has been associated with protection from invasive meningococcal disease (6) (7). Menactra induces the production of bactericidal antibodies specific to the capsular polysaccharides of serogroups A, C, Y and W-135.

## 13 NON-CLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Menactra has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility. A developmental animal toxicity study showed that Menactra had no effects on female fertility in mice [see *Pregnancy* (8.1)].

## 14 CLINICAL STUDIES

### 14.1 Efficacy

The serum bactericidal assay (SBA) used to test sera contained an exogenous complement source that was either human (SBA-H) or baby rabbit (SBA-BR). (8)



The response to vaccination following two doses of vaccine administered to children 9 and 12 months of age and following one dose of vaccine administered to children 2 through 10 years of age was evaluated by the proportion of participants having an SBA-H antibody titer of 1:8 or greater, for each serogroup. In individuals 11 through 55 years of age, the response to vaccination with a single dose of vaccine was evaluated by the proportion of participants with a 4-fold or greater increase in bactericidal antibody to each serogroup as measured by SBA-BR. For individuals 2 through 55 years of age, vaccine efficacy after a single dose was inferred from the demonstration of immunologic equivalence to a US-licensed meningococcal polysaccharide vaccine, Menomune – A/C/Y/W-135 vaccine as assessed by SBA.

## **14.2 Immunogenicity**

### ***Children 9 through 12 Months of Age***

In a randomized, US, multi-center trial, children received Menactra at 9 months and 12 months of age. The first Menactra dose was administered alone, followed by a second Menactra dose given alone (N=404), or with MMRV (N=302), or with PCV7 (N=422). For all participants, sera were obtained approximately 30 days after last vaccination. There were no substantive differences in demographic characteristics between the vaccine groups. The median age range for administration of the first dose of Menactra was 278-279 days of age.

**Table 5: Bactericidal Antibody Responses<sup>a</sup> 30 Days Following a Second Dose of Menactra Administered Alone or Concomitantly Administered with MMRV or PCV7 at 12 Months of Age**

		Vaccinations administered at 12 months of age following a dose of Menactra at 9 months of age					
		Menactra		Menactra + MMRV		Menactra + PCV7	
		(N=272-277) <sup>b</sup>		(N=177-180) <sup>b</sup>		(N=264-267) <sup>b</sup>	
Serogroup			(95% CI) <sup>c</sup>		(95% CI) <sup>c</sup>		(95% CI) <sup>c</sup>
<b>A</b>	% ≥1:8 <sup>d</sup>	95.6	(92.4; 97.7)	92.7	(87.8; 96.0)	90.5	(86.3; 93.8)
	GMT	54.9	(46.8; 64.5)	52.0	(41.8; 64.7)	41.0	(34.6; 48.5)
<b>C</b>	% ≥1:8 <sup>d</sup>	100.0	(98.7; 100.0)	98.9	(96.0; 99.9)	97.8	(95.2; 99.2)
	GMT	141.8	(123.5; 162.9)	161.9	(136.3; 192.3)	109.5	(94.1; 127.5)
<b>Y</b>	% ≥1:8 <sup>d</sup>	96.4	(93.4; 98.2)	96.6	(92.8; 98.8)	95.1	(91.8; 97.4)
	GMT	52.4	(45.4; 60.6)	60.2	(50.4; 71.7)	39.9	(34.4; 46.2)
<b>W-135</b>	% ≥1:8 <sup>d</sup>	86.4	(81.8; 90.3)	88.2	(82.5; 92.5)	81.2	(76.0; 85.7)
	GMT	24.3	(20.8; 28.3)	27.9	(22.7; 34.3)	17.9	(15.2; 21.0)

<sup>a</sup> Serum bactericidal assay with an exogenous human complement (SBA-H) source.

<sup>b</sup> N=Number of participants with at least one valid serology result from a blood sample obtained between Days 30 to 44 post vaccination.

<sup>c</sup> 95% CIs for the proportions are calculated based on the Clopper-Pearson Exact method and normal approximation for that of the GMTs.

<sup>d</sup> The proportion of participants achieving an SBA-H titer of at least 1:8 thirty days after the second dose of Menactra.

Administration of Menactra to children at 12 months and 15 months of age was evaluated in a US study. Prior to the first dose, 33.3% [n=16/48] of participants had an SBA-H titer  $\geq 1:8$  to Serogroup A, and 0-2% [n=0-1 of 50-51] to Serogroups C, Y and W-135. After the second dose, percentages of participants with an SBA-H titer  $\geq 1:8$  were: 85.2%, Serogroup A [n=46/54]; 100.0%, Serogroup C [n=54/54]; 96.3%, Serogroup Y [n=52/54]; 96.2%, Serogroup W-135 [n=50/52].

### ***Individuals 2 through 55 Years of Age***

Immunogenicity was evaluated in three comparative, randomized, US, multi-center, active controlled clinical trials that enrolled children (2 through 10 years of age), adolescents (11 through 18 years of age), and adults (18 through 55 years of age). Participants received a single dose of Menactra (N=2526) or Menomune – A/C/Y/W-135 (N=2317). For all age groups studied, sera were obtained before and approximately 28 days after vaccination. [Blinding procedures for safety assessments are described in *Adverse Reactions (6)*.]

In each of the trials, there were no substantive differences in demographic characteristics between the vaccine groups, between immunogenicity subsets or the overall study population. In the study of children 2 through 10 years of age, the median age of participants was 3 years; 95% completed the study. In the adolescent trial, the median age for both groups was 14 years; 99% completed the study. In the adult trial, the median age for both groups was 24 years; 94% completed the study.

1 *Immunogenicity in Children 2 through 10 Years of Age*

2 Of 1408 enrolled children 2 through 10 years of age, immune responses evaluated in a subset of  
3 Menactra participants (2 through 3 years of age, n=52; 4-10 years of age, n=84) and Menomune –  
4 A/C/Y/W-135 participants (2 through 3 years of age, n=53; 4-10 years of age, n=84) were  
5 comparable for all four serogroups ([Table 6](#)).  
6  
7

1 **Table 6: Comparison of Bactericidal Antibody Responses<sup>a</sup> to Menactra and Menomune –**  
2 **A/C/Y/W-135 28 Days after Vaccination for a Subset of Participants 2 through 3 Years of**  
3 **Age and 4 through 10 Years of Age**

		Ages 2 through 3 Years				Ages 4 through 10 Years			
		Menactra		Menomune – A/C/Y/W-135		Menactra		Menomune – A/C/Y/W-135	
		N <sup>b</sup> =48-52		N <sup>b</sup> =50-53		N <sup>b</sup> =84		N <sup>b</sup> =84	
Serogroup			(95% CI) <sup>c</sup>		(95% CI) <sup>c</sup>		(95% CI) <sup>c</sup>		(95% CI) <sup>c</sup>
A	% ≥1:8 <sup>d</sup>	73	(59,84)	64	(50,77)	81	(71,89)	55	(44,66)
	GMT	10	(8,13)	10	(7,12)	19	(14,26)	7	(6,9)
C	% ≥1:8 <sup>d</sup>	63	(48,76)	38	(25,53)	79	(68,87)	48	(37,59)
	GMT	27	(14,52)	11	(5,21)	28	(19,41)	12	(7,18)
Y	% ≥1:8 <sup>d</sup>	88	(75,95)	73	(59,84)	99	(94,100)	92	(84,97)
	GMT	51	(31,84)	18	(11,27)	99	(75,132)	46	(33,66)
W-135	% ≥1:8 <sup>d</sup>	63	(47,76)	33	(20,47)	85	(75,92)	79	(68,87)
	GMT	15	(9,25)	5	(3,6)	24	(18,33)	20	(14,27)

4 <sup>a</sup> Serum bactericidal assay with an exogenous human complement (SBA-H) source.

5 <sup>b</sup> N=Number of subset participants with at least one valid serology result at Day 0 and Day 28.

6 <sup>c</sup> The 95% CI for the Geometric Mean Titer (GMT) was calculated based on an approximation to the normal  
7 distribution.

8 <sup>d</sup> The proportion of participants achieving an SBA-H titer of at least 1:8 was assessed using a 10% non-inferiority  
9 margin and a one-sided Type 1 error rate of 0.025.

10

11 In the subset of participants 2 through 3 years of age with undetectable pre-vaccination titers (ie,  
12 SBA-H titers <1:4 at Day 0), seroconversion rates (defined as the proportions of participants with

SBA-H titers  $\geq 1:8$  by Day 28) were similar between the Menactra and Menomune – A/C/Y/W-135 recipients. Menactra participants achieved seroconversion rates of: 57%, Serogroup A (n=12/21); 62%, Serogroup C (n=29/47); 84%, Serogroup Y (n=26/31); 53%, Serogroup W-135 (n=20/38). The seroconversion rates for Menomune – A/C/Y/W-135 recipients were: 55%, Serogroup A (n=16/29); 30%, Serogroup C (n=13/43); 57%, Serogroup Y (n=17/30); 26%, Serogroup W-135 (n=11/43).

In the subset of participants 4 through 10 years of age with undetectable pre-vaccination titers (ie, SBA-H titers  $< 1:4$  at Day 0), seroconversion rates (defined as the proportions of participants with SBA-H titers  $\geq 1:8$  by Day 28) were similar between the Menactra and Menomune – A/C/Y/W-135 recipients. Menactra participants achieved seroconversion rates of: 69%, Serogroup A (n=11/16); 81%, Serogroup C (n=50/62); 98%, Serogroup Y (n=45/46); 69%, Serogroup W-135 (n=27/39). The seroconversion rates for Menomune – A/C/Y/W-135 recipients were: 48%, Serogroup A (n=10/21); 38%, Serogroup C (n=19/50); 84%, Serogroup Y (n=38/45); 68%, Serogroup W-135 (n=26/38).

### ***Immunogenicity in Adolescents 11 through 18 Years of Age***

Results from the comparative clinical trial conducted in 881 adolescents aged 11 through 18 years showed that the immune responses to Menactra and Menomune – A/C/Y/W-135 were similar for all four serogroups (Table 7).

In participants with undetectable pre-vaccination titers (ie, SBA-BR titers  $< 1:8$  at Day 0), seroconversion rates (defined as the proportions of participants achieving a  $\geq 4$ -fold rise in SBA-

BR titers by Day 28) were similar between the Menactra and Menomune – A/C/Y/W-135 recipients. Menactra participants achieved seroconversion rates of: 100%, Serogroup A (n=81/81); 99%, Serogroup C (n=153/155); 98%, Serogroup Y (n=60/61); 98%, Serogroup W-135 (n=161/164). The seroconversion rates for Menomune – A/C/Y/W-135 recipients were: 100%, Serogroup A (n=93/93); 99%, Serogroup C (n=151/152); 100%, Serogroup Y (n=47/47); 99%, Serogroup W-135 (n=138/139).

#### ***Immunogenicity in Adults 18 through 55 Years of Age***

Results from the comparative clinical trial conducted in 2554 adults aged 18 through 55 years showed that the immune responses to Menactra and Menomune – A/C/Y/W-135 were similar for all four serogroups (Table 7).



1 **Table 7: Comparison of Bactericidal Antibody Responses<sup>a</sup> to Menactra and Menomune –**  
2 **A/C/Y/W-135 28 Days after Vaccination for Participants 11 through 18 Years of Age and 18**  
3 **through 55 Years of Age**

		Ages 11 through 18 Years				Ages 18 through 55 Years			
		Menactra		Menomune – A/C/Y/W-135		Menactra		Menomune – A/C/Y/W-135	
		N <sup>b</sup> =423		N <sup>b</sup> =423		N <sup>b</sup> =1280		N <sup>b</sup> =1098	
Serogroup			(95% CI) <sup>c</sup>		(95% CI) <sup>c</sup>		(95% CI) <sup>c</sup>		(95% CI) <sup>c</sup>
<b>A</b>	% ≥4-fold rise <sup>d</sup>	92.7	(89.8, 95.0)	92.4	(89.5, 94.8)	80.5	(78.2, 82.6)	84.6	(82.3, 86.7)
	GMT	5483	(4920, 6111)	3246	(2910, 3620)	3897	(3647, 4164)	4114	(3832, 4417)
<b>C</b>	% ≥4-fold rise <sup>d</sup>	91.7	(88.7, 94.2)	88.7	(85.2, 91.5)	88.5	(86.6, 90.2)	89.7	(87.8, 91.4)
	GMT	1924	(1662, 2228)	1639	(1406, 1911)	3231	(2955, 3533)	3469	(3148, 3823)
<b>Y</b>	% ≥4-fold rise <sup>d</sup>	81.8	(77.8, 85.4)	80.1	(76.0, 83.8)	73.5	(71.0, 75.9)	79.4	(76.9, 81.8)
	GMT	1322	(1162, 1505)	1228	(1088, 1386)	1750	(1597, 1918)	2449	(2237, 2680)
<b>W-135</b>	% ≥4-fold rise <sup>d</sup>	96.7	(94.5, 98.2)	95.3	(92.8, 97.1)	89.4	(87.6, 91.0)	94.4	(92.8, 95.6)
	GMT	1407	(1232, 1607)	1545	(1384, 1725)	1271	(1172, 1378)	1871	(1723, 2032)

4 <sup>a</sup> Serum bactericidal assay with baby rabbit complement (SBA-BR).

5 <sup>b</sup> N=Number of subset participants with at least one valid serology result at Day 0 and Day 28.

6 <sup>c</sup> The 95% CI for the Geometric Mean Titer (GMT) was calculated based on an approximation to the normal  
7 distribution.

8 <sup>d</sup> Menactra was non-inferior to Menomune – A/C/Y/W-135. Non-inferiority was assessed by the proportion of  
9 participants with a 4-fold or greater rise in SBA-BR titer for *N meningitidis* serogroups A, C, Y and W-135 using a  
10 10% non-inferiority margin and a one-sided Type I error rate of 0.05.

1 In participants with undetectable pre-vaccination titers (ie, SBA-BR titers <1:8 at Day 0),  
2 seroconversion rates (defined as the proportions of participants achieving a  $\geq 4$ -fold rise in SBA-  
3 BR titers by Day 28) were similar between the Menactra and Menomune – A/C/Y/W-135  
4 recipients. Menactra participants achieved seroconversion rates of: 100%, Serogroup A  
5 (n=156/156); 99%, Serogroup C (n=343/345); 91%, Serogroup Y (n=253/279); 97%, Serogroup  
6 W-135 (n=360/373). The seroconversion rates for Menomune – A/C/Y/W-135 recipients were:  
7 99%, Serogroup A (n=143/144); 98%, Serogroup C (n=297/304); 97%, Serogroup Y  
8 (n=221/228); 99%, Serogroup W-135 (n=325/328).

#### 10 ***Immunogenicity in Adolescents and Adults Following Booster Vaccination***

11 For a description of the study design and number of participants, [see *Clinical Trials Experience*,  
12 *Booster Vaccination Study (6.1)*.] Prior to revaccination, the percentage of participants (n=781)  
13 with an SBA-H titer  $\geq 1:8$  were 64.5%, 44.2%, 38.7%, and 68.5% for Serogroups A, C, Y and W-  
14 135, respectively. Among the subset of trial participants (n=112) for whom SBA-H responses at  
15 Day 6 were assessed, 86.6%, 91.1%, 94.6%, and 92.0% achieved a  $\geq 4$ -fold rise in SBA-H titer for  
16 Serogroups A, C, Y and W-135, respectively. The proportions of participants (n=781) who  
17 achieved a  $\geq 4$ -fold rise in SBA-H titer by Day 28 were 95.0%, 95.3%, 97.1%, and 96% for  
18 Serogroups A, C, Y and W-135, respectively. The proportions of participants who achieved an  
19 SBA-H titer  $\geq 1:8$  by Day 28 were >99% for each serogroup.

#### 21 **14.3 Concomitant Vaccine Administration**

1 ***MMRV (or MMR + V) or PCV7***

2 In a US, active-controlled trial, 1179 children received Menactra at 9 months and 12 months of  
3 age. At 12 months of age these children received Menactra concomitantly with MMRV (N=616),  
4 or MMR + V (N=48), or PCV7 (N=250). Another group of 12-month old children received  
5 MMRV + PCV7 (N=485). Sera were obtained approximately 30 days after the last vaccinations.  
6 Measles, mumps, rubella and varicella antibody responses among children who received Menactra  
7 and MMRV (or MMR and V) were comparable to corresponding antibody responses among  
8 children who received MMRV and PCV7.

9  
10 When Menactra was given concomitantly with PCV7, the non-inferiority criteria for comparisons  
11 of pneumococcal IgG GMCs (upper limit of the two-sided 95% CI of the GMC ratio  $\leq 2$ ) were not  
12 met for 3 of 7 serotypes (4, 6B, 18C). In a subset of participants with available sera,  
13 pneumococcal opsonophagocytic assay GMT data were consistent with IgG GMC data.

14  
15 ***Td Vaccine***

16 In a double-blind, randomized, controlled trial, 1021 participants aged 11 through 17 years  
17 received Td vaccine and Menactra concomitantly (N=509), or Td vaccine followed one month  
18 later by Menactra (N=512). Sera were obtained approximately 28 days after each respective  
19 vaccination. The proportions of participants with a 4-fold or greater increase in SBA-BR titer to  
20 meningococcal Serogroups C, Y and W-135 were higher when Menactra was given concomitantly  
21 with Td vaccine (86%-96%) than when Menactra was given one month following Td vaccine  
22 (65%-91%). Anti-tetanus and anti-diphtheria antibody responses were similar in both study  
23 groups.

***Typhim Vi***

In a double-blind, randomized, controlled trial, 945 participants aged 18 through 55 years received Typhim Vi and Menactra concomitantly (N=469), or Typhim Vi followed one month later by Menactra (N=476). Sera were obtained approximately 28 days after each respective vaccination. The antibody responses to Menactra and to Typhim Vi components were similar in both study groups.

***DAPTACEL and IPV***

In a randomized, parallel group, US multi-center clinical trial conducted in children 4 through 6 years of age, Menactra was administered as follows: 30 days after concomitant DTaP (DAPTACEL<sup>®</sup>, Sanofi Pasteur Limited) + IPV (IPOL<sup>®</sup>, Sanofi Pasteur SA) [Group A]; concomitantly with DAPTACEL followed 30 days later by IPV [Group B]; concomitantly with IPV followed 30 days later by DAPTACEL [Group C]. Sera were obtained approximately 30 days after each respective vaccination. [See *Clinical Trials Experience* (6.1).]

When Menactra was administered 30 days after DAPTACEL (and IPV) [Group A], significantly lower SBA-H GMTs to all 4 meningococcal serogroups were observed compared to Menactra (and IPV) administered 30 days prior to DAPTACEL [Group C]. When Menactra was administered concomitantly with DAPTACEL [Group B], SBA-H GMTs to meningococcal serogroups A, C, and W-135 were non-inferior to those observed after Menactra (and IPV) [Group C]. The non-inferiority criterion was marginally missed for meningococcal serogroup Y. Non-inferiority of SBA-H GMTs following concomitant administration of Menactra and

1 DAPTACEL compared to those after concomitant Menactra and IPV was concluded if the upper  
2 limit of the 2-sided 95% CI of ( $\text{GMT}_{\text{Group C}}$  divided by  $\text{GMT}_{\text{Group B}}$ ) computed separately for each  
3 of the serogroups was  $<2$ .

4  
5 The respective SBA-H GMTs and proportion (%) of Group A, B, and C study participants  
6 achieving an SBA-H titer of  $\geq 1:8$  are displayed in [Table 8](#).

1 **Table 8: Bactericidal Antibody Responses<sup>a</sup> 30 Days Following Menactra Administered**  
 2 **Alone or Concomitantly with DAPTACEL or IPV**

		Vaccines administered at Visit 1 and 30 days later at Visit 2					
	Visit 1 Visit 2	Group A DAPTACEL + IPV Menactra		Group B Menactra + DAPTACEL IPV		Group C Menactra + IPV DAPTACEL	
		(N=250) <sup>b</sup>		(N=238) <sup>b</sup>		(N=121) <sup>b</sup>	
Serogroup			(95% CI) <sup>c</sup>		(95% CI) <sup>c</sup>		(95% CI) <sup>c</sup>
<b>A</b>	% ≥ 1:8 <sup>d</sup>	49.6	(41.0; 58.3)	67.2	(58.4; 75.1)	64.4	(54.4; 73.6)
	GMT	6.7	(5.7; 8.0)	10.8	(8.7; 13.3)	10.4	(8.1; 13.3)
<b>C</b>	% ≥ 1:8 <sup>d</sup>	20.3	(13.9; 28.0)	50.4	(41.5; 59.2)	50.5	(40.5; 60.5)
	GMT	3.3	(2.7; 3.9)	8.1	(6.3; 10.5)	7.8	(5.8; 10.7)
<b>Y</b>	% ≥ 1:8 <sup>d</sup>	44.2	(35.8; 52.9)	80.2	(72.3; 86.6)	88.5	(80.7; 93.9)
	GMT	6.5	(5.1; 8.2)	18.1	(14.2; 22.9)	26.2	(20.0; 34.4)
<b>W-135</b>	% ≥ 1:8 <sup>d</sup>	55.1	(46.4; 63.5)	87.8	(80.9; 92.9)	82.7	(74.0; 89.4)
	GMT	8.4	(6.7; 10.6)	22.8	(18.5; 28.1)	21.7	(16.6; 28.4)

- 3 <sup>a</sup> Serum bactericidal assay with an exogenous human complement (SBA-H) source.
- 4 <sup>b</sup> N=Total number of the subjects in the study population per group.
- 5 <sup>c</sup> 95% CIs for the proportions are calculated based on the Clopper-Pearson Exact method and normal approximation
- 6 for that of the GMTs.
- 7 <sup>d</sup> The proportion of participants achieving an SBA-H titer of at least 1:8, 30 days after Menactra.

8

1 When Menactra was administered concomitantly with DAPTACEL, antibody responses to three  
2 of the pertussis antigens (pertussis toxin, filamentous hemagglutinin, and pertactin) (GMCs),  
3 tetanus toxin (% participants with antibody concentrations  $\geq 1.0$  IU/mL), and diphtheria toxin (%  
4 participants with antibody concentrations  $\geq 1.0$  IU/mL) were non-inferior to those observed after  
5 DAPTACEL and IPV. The pertussis anti-fimbriae GMCs were marginally lower when Menactra  
6 and DAPTACEL were administered concomitantly.

7



## 15 REFERENCES

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## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

- Single-dose vial, 0.5 mL (NDC 49281-589-58). Supplied as a package of 5 vials (NDC 49281-589-05).

### 16.2 Storage and Handling

Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Frozen/previously frozen product should not be used. Do not use after the expiration date.

## 17 PATIENT COUNSELING INFORMATION

Vaccine Information Statements are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization to the patient, parent, or guardian. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).

Inform the patients, parents or guardians about:

- Potential benefits and risks of immunization with Menactra.
- Potential for adverse reactions that have been temporally associated with administration of Menactra or other vaccines containing similar components.
- Reporting any adverse reactions to their healthcare provider.
- The Sanofi Pasteur Inc. Pregnancy Registry, as appropriate [see *Pregnancy* (8.1)].

Menactra® is a registered trademark of Sanofi, its affiliates and subsidiaries.

Manufactured by:

**Sanofi Pasteur Inc.**

Swiftwater PA 18370 USA

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SANOFI PASTEUR 

# **EXHIBIT 261**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use MENVEO safely and effectively. See full prescribing information for MENVEO.

**MENVEO [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM<sub>197</sub> Conjugate Vaccine] for injection, for intramuscular use**  
Initial U.S. Approval: 2010

**RECENT MAJOR CHANGES**

Dosage and Administration (2.1, 2.2)	09/2019
Dosage and Administration, Dosing Schedule (2.3)	12/2019

**INDICATIONS AND USAGE**

MENVEO is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y, and W-135. MENVEO is approved for use in persons aged 2 months through 55 years. MENVEO does not prevent *N. meningitidis* serogroup B infections. (1)

**DOSAGE AND ADMINISTRATION**

- For intramuscular injection only (0.5 mL). (2)
- MENVEO is supplied in 2 vials that must be combined prior to administration: reconstitute the MenA lyophilized conjugate vaccine component with the MenCYW-135 liquid conjugate vaccine component immediately before administration. (2.1)

**Primary Vaccination**

- In children initiating vaccination at 2 months of age, MENVEO is to be administered as a 4-dose series at 2, 4, 6, and 12 months of age. (2.3)
- In children initiating vaccination at 7 months through 23 months of age, MENVEO is to be administered as a 2-dose series with the second dose administered in the second year of life and at least 3 months after the first dose. (2.3)
- In individuals aged 2 through 55 years MENVEO is to be administered as a single dose. (2.3)

**Booster Vaccination**

- A single booster dose of MENVEO may be administered to individuals aged 15 through 55 years who are at continued risk for meningococcal disease if at least 4 years have elapsed since a prior dose of a meningococcal (serogroups A, C, Y, W-135) conjugate vaccine. (2.3)

**DOSAGE FORMS AND STRENGTHS**

Solution for intramuscular injection supplied as a lyophilized MenA conjugate vaccine component to be reconstituted with the accompanying MenCYW-135 liquid conjugate vaccine component. A single dose after reconstitution is 0.5 mL. (3)

**CONTRAINDICATIONS**

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of MENVEO, any component of this vaccine, or any other CRM<sub>197</sub>-, diphtheria toxoid-, or meningococcal-containing vaccine is a contraindication to administration of MENVEO. (4)

**WARNINGS AND PRECAUTIONS**

- Appropriate medical treatment must be available should an acute allergic reaction, including an anaphylactic reaction, occur following administration of MENVEO. (5.1)
- Syncope, sometimes resulting in falling injury, has been reported following vaccination with MENVEO. Vaccinees should be observed for at least 15 minutes after vaccine administration. (5.2)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including MENVEO, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.5)

**ADVERSE REACTIONS**

- Common solicited adverse reactions (≥10%) among children initiating vaccination at 2 months of age and receiving the 4-dose series were tenderness (24% to 41%) and erythema at injection site (11% to 15%), irritability (42% to 57%), sleepiness (29% to 50%), persistent crying (21% to 41%), change in eating habits (17% to 23%), vomiting (5% to 11%), and diarrhea (8% to 16%). (6.1)
- Common solicited adverse reactions (≥10%) among children initiating vaccination at 7 months through 23 months of age and receiving the 2-dose series were tenderness (10% to 16%) and erythema at injection site (12% to 15%), irritability (27% to 40%), sleepiness (17% to 29%), persistent crying (12-21%), change in eating habits (12% to 20%), and diarrhea (10% to 16%). (6.1)
- Common solicited adverse reactions (≥10%) among children aged 2 through 10 years who received MENVEO were injection site pain (31%), erythema (23%), irritability (18%), induration (16%), sleepiness (14%), malaise (12%), and headache (11%). (6.1)
- Common solicited adverse reactions (≥10%) among adolescents and adults who received a single dose of MENVEO were pain at the injection site (41%), headache (30%), myalgia (18%), malaise (16%), and nausea (10%). Similar rates of solicited adverse reactions were observed following a single booster dose. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).**

**DRUG INTERACTIONS**

Do not mix MENVEO or any of its components with any other vaccine or diluent in the same syringe or vial. (7.1)

**See 17 for PATIENT COUNSELING INFORMATION.**

Revised: 01/2020

**FULL PRESCRIBING INFORMATION: CONTENTS\***

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- 2 DOSAGE AND ADMINISTRATION
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\*Sections or subsections omitted from the full prescribing information are not listed.

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

MENVEO is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y, and W-135. MENVEO is approved for use in persons aged 2 months through 55 years.

MENVEO does not prevent *N. meningitidis* serogroup B infections.

### **2 DOSAGE AND ADMINISTRATION**

**For intramuscular injection only.**

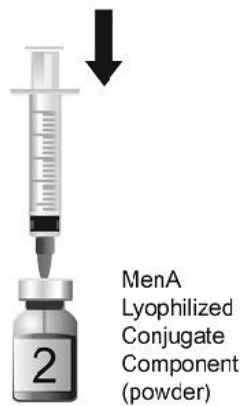
#### **2.1 Reconstitution**

MENVEO is supplied in 2 vials that must be combined prior to administration. Use the MenCYW-135 liquid conjugate vaccine component (Vial 1) to reconstitute the MenA lyophilized conjugate vaccine component (Vial 2) to form MENVEO. Invert the vial and shake well until the vaccine is dissolved and then withdraw 0.5 mL of reconstituted product. Following reconstitution, the vaccine is a clear, colorless solution, free from visible foreign particles.

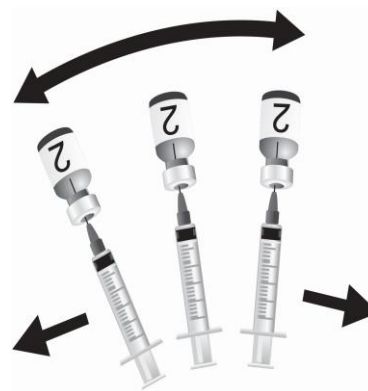
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If any of these conditions exist, MENVEO should not be administered.



**Figure 1.** Cleanse both vial stoppers. Using a sterile needle and sterile graduated syringe, withdraw the entire contents of Vial 1 containing the MenCYW-135 liquid conjugate component while slightly tilting the vial.



**Figure 2.** Slowly transfer entire contents of the syringe into Vial 2 containing the MenA lyophilized conjugate component (powder).



**Figure 3.** Invert the vial and shake well until powder is completely dissolved.



**Figure 4.** After reconstitution, withdraw 0.5 mL from the vial containing the reconstituted vaccine. Administer **intramuscularly**.

Please note that it is normal for a small amount of liquid to remain in the vial following withdrawal of the dose. Discard unused portion.

## 2.2 Administration Instructions

### **For intramuscular injection only.**

After reconstitution, administer MENVEO immediately or store between 36°F and 77°F (2°C and 25°C) for up to 8 hours. Shake well before using. Do not freeze. Discard reconstituted vaccine if it has been frozen or not used within 8 hours.

Use a separate sterile needle and sterile syringe for each individual. Each dose of MENVEO should be administered as a single 0.5-mL intramuscular injection, preferably into the anterolateral aspect of the thigh in infants or into the deltoid muscle (upper arm) in toddlers, adolescents, and adults. Do not administer MENVEO intravenously, subcutaneously, or intradermally.



## **2.3 Dosing Schedule**

**The dosing schedule is as follows:**

### **Primary Vaccination**

*Infants Aged 2 Months:* MENVEO is to be administered as a 4-dose series at 2, 4, 6, and 12 months of age.

*Children Aged 7 through 23 Months:* MENVEO is to be administered as a 2-dose series with the second dose administered in the second year of life and at least 3 months after the first dose.

*Children Aged 2 through 10 Years:* MENVEO is to be administered as a single dose. For children aged 2 through 5 years at continued high risk of meningococcal disease, a second dose may be administered 2 months after the first dose.

*Adolescents and Adults Aged 11 through 55 Years:* MENVEO is to be administered as a single dose.

### **Booster Vaccination**

*Adolescents and Adults Aged 15 through 55 Years:* A single booster dose of MENVEO may be administered to individuals who are at continued risk for meningococcal disease if at least 4 years have elapsed since a prior dose of a meningococcal (serogroups A, C, Y, W-135) conjugate vaccine.

## **3 DOSAGE FORMS AND STRENGTHS**

MENVEO is a solution for intramuscular injection supplied as a lyophilized MenA conjugate vaccine component to be reconstituted with the accompanying MenCYW-135 liquid conjugate vaccine component. A single dose, after reconstitution, is 0.5 mL. *[See Dosage and Administration (2), How Supplied/Storage and Handling (16).]*

## **4 CONTRAINDICATIONS**

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of MENVEO, any component of this vaccine, or any other CRM<sub>197</sub>-, diphtheria toxoid-, or meningococcal-containing vaccine is a contraindication to administration of MENVEO. *[See Description (11).]*

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Management of Acute Allergic Reactions**

Appropriate medical treatment must be available should an acute allergic reaction, including an anaphylactic reaction, occur following administration of MENVEO.

## 5.2 Syncope

Syncope, sometimes resulting in falling injury associated with seizure-like movements, has been reported following vaccination with MENVEO. Vaccinees should be observed for at least 15 minutes after vaccine administration to prevent and manage syncopal reactions.

## 5.3 Altered Immunocompetence

### Reduced Immune Response

Some individuals with altered immunocompetence, including some individuals receiving immunosuppressant therapy, may have reduced immune responses to MENVEO.

### Complement Deficiency

Persons with certain complement deficiencies and persons receiving treatment that inhibits terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *N. meningitidis*, including invasive disease caused by serogroups A, C, Y, and W, even if they develop antibodies following vaccination with MENVEO. [See *Clinical Pharmacology* (12.1).]

## 5.4 Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) has been reported in temporal relationship following administration of another U.S.-licensed meningococcal quadrivalent polysaccharide conjugate vaccine. The decision to administer MENVEO to subjects with a known history of Guillain-Barré Syndrome should take into account the potential benefits and risks.

## 5.5 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including MENVEO, to an infant born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination.

# 6 ADVERSE REACTIONS

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

### Primary Vaccination Studies

*Children Aged 2 through 23 Months:* The safety of MENVEO in infants vaccinated at 2, 4, 6, and 12 months of age was evaluated in 3 randomized multicenter clinical studies<sup>1-3</sup> conducted in the U.S., Australia, Canada, Taiwan, and several countries of Latin America in which 8,735 infants received at least 1 dose of MENVEO and routine infant vaccines (diphtheria toxoid;

acellular pertussis; tetanus toxoid; inactivated polio types 1, 2, and 3; hepatitis B; *Haemophilus influenzae* type b (Hib) antigens; pentavalent rotavirus; and 7-valent pneumococcal conjugate). With Dose 4 of MENVEO, toddlers received concomitantly the following vaccines: 7-valent pneumococcal conjugate; measles, mumps, rubella, and varicella; and inactivated hepatitis A. A total of 2,864 infants in these studies received the routine infant/toddler vaccines only. The infants who received MENVEO were Caucasian (33%), Hispanic (44%), African American (8%), Asian (8%), and other racial/ethnic groups (7%); 51% were male, with a mean age of 65.1 days (Standard Deviation [SD]: 7.5 days) at the time of first vaccination.

Safety data for administration of 2 doses of MENVEO in children aged 6 through 23 months are available from 3 randomized studies<sup>1,4,5</sup> conducted in the U.S., Latin America, and Canada, of which one U.S. study specifically addressed the safety of MENVEO administered concomitantly with measles, mumps, rubella, and varicella vaccine (MMRV). The 1,985 older infants and toddlers who received 2 doses of MENVEO were Caucasian (49%), Hispanic (32%), African American (11%), and other racial/ethnic groups (8%), 51% male, with a mean age of 10.1 months (SD: 2.0 months).

*Children Aged 2 through 10 Years:* The safety of MENVEO in children aged 2 through 10 years was evaluated in 4 clinical trials<sup>6-9</sup> conducted in North America (66%), Latin America (28%), and Europe (6%) in which 3,181 subjects received MENVEO and 2,116 subjects received comparator vaccines (either Meningococcal Polysaccharide Vaccine, Groups A, C, Y, and W-135 Combined - MENOMUNE, Sanofi Pasteur [n = 861], or Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine - MENACTRA, Sanofi Pasteur [n = 1,255]). The subjects aged 2 through 10 years who received MENVEO were Caucasian (69%), Hispanic (13%), African American (7%), and other racial/ethnic groups (6%), 51% male, with a mean age of 5.2 years. The safety of a second dose of MENVEO administered 2 months following a first dose was studied in 351 children aged 2 through 5 years.

*Adolescents and Adults:* The safety of MENVEO in individuals aged 11 through 55 years was evaluated in 5 randomized controlled clinical trials<sup>10-14</sup> in which 6,185 participants received MENVEO alone (5,286 participants), MENVEO concomitant with other vaccine(s) (899 participants), or a U.S.-licensed comparator vaccine (1,966 participants). In the concomitant trials<sup>11,14</sup> MENVEO was given with vaccines containing: tetanus toxoid, diphtheria toxoid, and pertussis (Tdap), or Tdap with human papillomavirus (HPV). The comparator vaccine was either MENOMUNE (209 participants) or MENACTRA (1,757 participants). The trials were conducted in North America (46%), Latin America (41%), and Europe (13%). In 2 of the studies, subjects received concomitant vaccination with Tdap or with Tdap plus HPV. Overall, subjects were Caucasian (50%), followed by Hispanic (40%), African American (7%), and other racial/ethnic groups (3%). Among recipients of MENVEO, 61%, 17%, and 22% were in the 11-through 18-year, 19-through 34-year, and 35-through 55-year age groups, respectively, with a mean age of 23.5 years (SD: 12.9 years). Among recipients of MENACTRA, 31%, 32%, and 37% were in the 11-through 18-year, 19-through 34-year, and 35-through 55-year age groups,

respectively, with a mean age of 29.2 years (SD: 13.4 years). Among MENOMUNE recipients, 100% were in the 11- through 18-year age group, and the mean age was 14.2 years (SD: 1.8 years).

#### Booster Vaccination Study

In a multicenter, open-label trial (NCT02986854)<sup>15</sup> conducted in the U.S., 601 subjects aged 15 to 51 years received a single booster dose of MENVEO 4 to 6 years after prior vaccination with MENVEO (n = 301; median age: 16 years) or MENACTRA (n = 300; median age: 16 years). Across booster groups of MENVEO, 81% of subjects were white and 50% were female.

In most trials, solicited local and systemic adverse reactions were monitored daily for 7 days following each (one or more) vaccination and recorded on a diary card. Participants were monitored for unsolicited adverse events which included adverse events requiring a physician visit or Emergency Department visit (i.e., medically-attended) or which led to a subject's withdrawal from the study. Among children, adolescents, and adults aged 2 to 55 years, medically significant adverse events and serious adverse events (SAE) were monitored for 6 months after vaccination. Across the studies of infants and toddlers aged 2 through 23 months, either all medically-attended or all medically-significant adverse events were collected in the period between the infant dose(s) and the toddler doses and during the 6-month period after the toddler dose.

#### Solicited Adverse Reactions in the Primary Vaccination Studies

The reported frequencies of solicited local and systemic adverse reactions from U.S. infants in the largest multinational safety study of MENVEO<sup>2</sup> are presented in Table 1. Among the U.S. participants in the group receiving MENVEO with routine vaccines, 51% were female; 64% were Caucasian, 12% were African American, 15% were Hispanic, 2% were Asian, and 7% were of other racial/ethnic groups.

In infants initiating vaccination at 2 months of age and receiving the 4-dose series, common solicited adverse reactions ( $\geq 10\%$ ) were tenderness (24% to 41%) and erythema at injection site (11% to 15%), irritability (42% to 57%), sleepiness (29% to 50%), persistent crying (21% to 41%), change in eating habits (17% to 23%), vomiting (5% to 11%), and diarrhea (8% to 16%). The rates of solicited adverse reactions reported for subjects aged 2 months and older receiving MENVEO with routine vaccines at 2, 4, 6, and 12 months of age were comparable to rates among subjects who only received routine vaccines.

**Table 1. Rates of Solicited Adverse Reactions Reported in U.S. Infants, Aged 2 Months and Older, during the 7 Days following Each Vaccination of MENVEO Administered with Routine Infant/Toddler Vaccines, or Routine Infant/Toddler Vaccines Alone at 2, 4, 6, and 12 Months of Age<sup>a</sup>**

Adverse Reactions	Dose 1		Dose 2		Dose 3		Dose 4	
	MENVEO with Routine <sup>b</sup> %	Routine Vaccines <sup>b</sup> %	MENVEO with Routine <sup>b</sup> %	Routine Vaccines <sup>b</sup> %	MENVEO with Routine <sup>b</sup> %	Routine Vaccines <sup>b</sup> %	MENVEO with Routine <sup>b</sup> %	Routine Vaccines <sup>b</sup> %
<b>Local Adverse Reactions<sup>c</sup></b>	<b>n = 1,250-1,252</b>	<b>n = 428</b>	<b>n = 1,205-1,207</b>	<b>n = 399</b>	<b>n = 1,056-1,058</b>	<b>n = 351-352</b>	<b>n = 1,054-1,055</b>	<b>n = 334-337</b>
Tenderness, any	41	45	31	36	24	32	29	39
Tenderness, severe <sup>d</sup>	3	5	2	2	1	3	1	1
Erythema, any	11	14	12	21	14	23	15	25
Erythema, >50 mm	<1	<1	0	0	0	0	0	0
Induration, any	8	16	9	17	8	19	8	21
Induration, >50 mm	0	<1	0	0	0	0	0	0
<b>Systemic Adverse Reactions</b>	<b>n = 1,246-1,251</b>	<b>n = 427-428</b>	<b>n = 1,119-1,202</b>	<b>n = 396-398</b>	<b>n = 1,050-1,057</b>	<b>n = 349-350</b>	<b>n = 1,054-1,056</b>	<b>n = 333-337</b>
Irritability, any	57	59	48	46	42	38	43	42
Irritability, severe <sup>e</sup>	2	2	1	3	1	1	2	1
Sleepiness, any	50	50	37	36	30	30	29	27
Sleepiness, severe <sup>f</sup>	2	1	1	1	<1	<1	1	0
Persistent crying, any	41	38	28	24	22	17	21	18
Persistent crying, ≥3 hours	2	2	2	2	1	1	1	1
Change in eating habits, any	23	24	18	17	17	13	19	16
Change in eating habits, severe <sup>g</sup>	1	1	1	1	1	<1	1	0
Vomiting, any	11	9	7	6	6	4	5	4
Vomiting, severe <sup>h</sup>	<1	0	<1	0	<1	0	<1	0
Diarrhea, any	16	11	11	8	8	6	13	9
Diarrhea, severe <sup>i</sup>	<1	<1	<1	<1	1	<1	1	1
Rash <sup>j</sup>	3	3	3	4	3	3	4	3
Fever ≥38.0°C <sup>k</sup>	3	2	4	6	7	6	9	7
Fever 38.0-38.9°C	3	2	4	5	7	6	6	5
Fever 39.0-39.9°C	0	0	1	1	<1	0	2	2

Fever $\geq 40.0^{\circ}\text{C}$	0	<1	0	<1	0	0	<1	0
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Clinicaltrials.gov Identifier NCT00806195.<sup>2</sup>

n = Number of subjects who completed the diary card for a given symptom at the specified vaccination.

<sup>a</sup> As-Treated Safety Subpopulation = U.S. children who received at least 1 dose of study vaccine and whose diary cards were completed per protocol and returned to the site.

<sup>b</sup> Routine infant/toddler vaccines include DTaP-IPV-Hib and PCV7 at Doses 1, 2, 3, and PCV7, MMRV, and Hepatitis A vaccines at Dose 4. HBV and rotavirus vaccines were allowed according to Advisory Committee on Immunization Practices (ACIP) recommendations.

<sup>c</sup> Local reactogenicity of MENVEO and PCV7 was assessed.

<sup>d</sup> Tenderness, severe = Cried when injected limb moved.

<sup>e</sup> Irritability, severe = Unable to console.

<sup>f</sup> Sleepiness, severe = Sleeps most of the time, hard to arouse.

<sup>g</sup> Change in eating habits, severe = Missed >2 feeds.

<sup>h</sup> Vomiting, severe = Little/no intake for more prolonged time.

<sup>i</sup> Diarrhea, severe =  $\geq 6$  liquid stools, no solid consistency.

<sup>j</sup> Rash was assessed only as present or not present, without a grading for severity.

<sup>k</sup> Axillary temperature.

The safety of a second dose of MENVEO administered at 12 months of age concomitantly with MMRV was investigated in a randomized, controlled, multicenter study<sup>5</sup> conducted in the U.S. The rates of solicited adverse reactions reported were comparable between the concomitantly administered group (MENVEO with MMRV) and the group which received MMRV alone or MENVEO alone. The frequency and severity of solicited local and systemic reactions occurring within 7 days following vaccination at 12 months of age are shown in Table 2. In subjects who received both MENVEO and MMRV at 12 months of age local reactions at both injection sites were evaluated separately. Body temperature measurements were collected for 28 days following the 12-months-of-age visit, when MMRV was administered to the vaccinees. Common solicited adverse reactions ( $\geq 10\%$ ) among children initiating vaccination at 7 months through 23 months of age and receiving the 2-dose series were tenderness (10% to 16%) and erythema at injection site (12% to 15%), irritability (27% to 40%), sleepiness (17% to 29%), persistent crying (12% to 21%), change in eating habits (12% to 20%), and diarrhea (10% to 16%). An examination of the fever profile during this period showed that MENVEO administered with MMRV did not increase the frequency or intensity of fever above that observed for the MMRV-only group.

**Table 2. Rates of Solicited Adverse Reactions Reported in U.S. Toddlers during the 7 Days following Vaccination with MENVEO Administered at 7-9 Months and 12 Months of Age, MENVEO Administered Alone at 7-9 Months and with MMRV at 12 Months of Age, and MMRV Administered Alone at 12 Months of Age<sup>a</sup>**

Adverse Reactions	MENVEO		MENVEO + MMRV		MMRV
	MENVEO 7-9 Months %	MENVEO 12 Months %	MENVEO 7-9 Months %	MENVEO with MMRV 12 Months %	MMRV 12 Months %
<b>Local Adverse Reactions– MENVEO</b>	<b>n = 460-462</b>	<b>n = 381-384</b>	<b>n = 430-434</b>	<b>n = 386-387</b>	
Tenderness, any	11	10	11	16	N/A
Tenderness, severe <sup>b</sup>	<1	<1	<1	0	N/A
Erythema, any	15	13	13	12	N/A
Erythema, >50 mm	<1	<1	0	1	N/A
Induration, any	8	8	7	8	N/A
Induration, >50 mm	<1	<1	0	1	N/A
<b>Local Adverse Reactions– MMRV</b>				<b>n = 382-383</b>	<b>n = 518-520</b>
Tenderness, any	N/A	N/A	N/A	16	19
Tenderness, severe <sup>b</sup>	N/A	N/A	N/A	0	<1
Erythema, any	N/A	N/A	N/A	15	14
Erythema, >50 mm	N/A	N/A	N/A	1	<1
Induration, any	N/A	N/A	N/A	13	8
Induration, >50 mm	N/A	N/A	N/A	<1	0
<b>Systemic Adverse Reactions</b>	<b>n = 461-463</b>	<b>n = 385-386</b>	<b>n = 430-434</b>	<b>n = 387-389</b>	<b>n = 522-524</b>
Irritability, any	40	27	37	37	44
Irritability, severe <sup>c</sup>	2	2	2	1	3
Sleepiness, any	26	17	29	26	32
Sleepiness, severe <sup>d</sup>	2	1	1	1	2
Persistent crying, any	21	12	20	19	20
Persistent crying, ≥3 hours	2	1	1	1	2
Change in eating habits, any	17	12	17	20	20
Change in eating habits, severe <sup>e</sup>	<1	1	1	2	1
Vomiting, any	9	6	9	6	6
Vomiting, severe <sup>f</sup>	<1	<1	<1	<1	<1
Diarrhea, any	16	10	15	15	20
Diarrhea, severe <sup>g</sup>	2	1	<1	1	2
Rash <sup>h</sup>	3	5	6	6	8
Fever ≥38.0°C <sup>i</sup>	5	5	6	9	7
Fever 38.0-38.9°C	3	3	5	7	7
Fever 39.0-39.9°C	2	2	1	1	1
Fever ≥40.0°C	<1	1	<1	<1	0

Clinicaltrials.gov Identifier NCT00626327.<sup>5</sup>

n = Number of subjects who completed the diary card for a given symptom at the specified vaccination.

<sup>a</sup> As-Treated Safety Subpopulation = U.S. children who received at least 1 dose of study vaccine and whose diary cards were completed per protocol and returned to the site.



- <sup>b</sup> Tenderness, severe = Cried when injected limb moved.
- <sup>c</sup> Irritability, severe = Unable to console.
- <sup>d</sup> Sleepiness, severe = Sleeps most of the time, hard to arouse.
- <sup>e</sup> Change in eating habits, severe = Missed >2 feeds.
- <sup>f</sup> Vomiting, severe = Little/no intake for more prolonged time.
- <sup>g</sup> Diarrhea, severe =  $\geq 6$  liquid stools, no solid consistency.
- <sup>h</sup> Rash was assessed only as present or not present, without a grading for severity.
- <sup>i</sup> Axillary temperature.

In clinical trials of children aged 2 through 10 years,<sup>6-9</sup> the most frequently occurring adverse reactions ( $\geq 10\%$ ) among all subjects who received MENVEO were injection site pain (31%), erythema (23%), irritability (18%), induration (16%), sleepiness (14%), malaise (12%), and headache (11%). Among subjects aged 11 through 55 years, the most frequently occurring adverse reactions ( $\geq 10\%$ ) among all subjects who received MENVEO were pain at the injection site (41%), headache (30%), myalgia (18%), malaise (16%), and nausea (10%).

The rates of solicited adverse reactions reported for subjects aged 2 through 5 years and 6 through 10 years who received a single dose of MENVEO or MENACTRA in a randomized, controlled, multicenter study<sup>9</sup> conducted in the U.S. and Canada are shown in Table 3. Following a second dose of MENVEO administered to children aged 2 through 5 years, the most common solicited adverse reactions ( $\geq 10\%$ ) were pain at injection site (28%), erythema (22%), irritability (16%), induration (13%), and sleepiness (12%). The solicited adverse reactions from a separate randomized, controlled, multicenter study conducted in the U.S. in adolescents and adults<sup>12</sup> are provided in Tables 4 and 5, respectively. In neither study were concomitant vaccines administered with the study vaccines.

**Table 3. Rates of Solicited Adverse Reactions within 7 Days following a Single Vaccination in Children Aged 2 through 5 Years and 6 through 10 Years**

Adverse Reactions	Participants Aged 2 through 5 Years					
	MENVEO n = 693 %			MENACTRA n = 684 %		
	Any	Moderate	Severe	Any	Moderate	Severe
<b>Local Adverse Reactions</b>						
Injection site pain <sup>a</sup>	33	6	1	35	8	0.4
Erythema <sup>b</sup>	27	5	1	25	3	0.3
Induration <sup>b</sup>	18	2	0.4	18	2	0.3
<b>Systemic Adverse Reactions<sup>e</sup></b>						
Irritability <sup>a</sup>	21	6	1	22	7	1
Sleepiness <sup>a</sup>	16	3	1	18	5	1
Change in eating <sup>a</sup>	9	2	1	10	2	0.3

Diarrhea <sup>a</sup>	7	1	0.1	8	1	0
Headache <sup>a</sup>	5	1	0	6	1	0.3
Rash <sup>c</sup>	4	-	-	5	-	-
Arthralgia <sup>a</sup>	3	1	0.1	4	1	0
Vomiting <sup>a</sup>	3	1	0.1	3	1	0
Fever <sup>d</sup>	2	0.4	0	2	0.3	0
<b>Participants Aged 6 through 10 Years</b>						
<b>Adverse Reactions</b>	<b>MENVEO n = 582 %</b>			<b>MENACTRA n = 571 %</b>		
	<b>Any</b>	<b>Moderate</b>	<b>Severe</b>	<b>Any</b>	<b>Moderate</b>	<b>Severe</b>
<b>Local Adverse Reactions</b>						
Injection site pain <sup>a</sup>	39	8	1	45	10	2
Erythema <sup>b</sup>	28	5	1	22	2	0.2
Induration <sup>b</sup>	17	2	0.3	13	2	0
<b>Systemic Adverse Reactions<sup>e</sup></b>						
Headache <sup>a</sup>	18	3	1	13	2	1
Malaise <sup>a</sup>	14	3	1	11	3	1
Myalgia <sup>a</sup>	10	2	1	10	2	1
Nausea <sup>a</sup>	8	2	1	6	2	0.4
Arthralgia <sup>a</sup>	6	1	0	4	1	0.4
Chills <sup>a</sup>	5	1	0	5	1	0.4
Rash <sup>c</sup>	5	-	-	3	-	-
Fever <sup>d</sup>	2	1	0	2	0	0.4

Clinicaltrials.gov Identifier NCT00616421.<sup>9</sup>

<sup>a</sup> Moderate: Some limitation in normal daily activity, Severe: Unable to perform normal daily activity.

<sup>b</sup> Moderate:  $\geq 50$ -100 mm, Severe:  $>100$  mm.

<sup>c</sup> Rash was assessed only as present or not present, without a grading for severity.

<sup>d</sup> Fever grading: Any:  $\geq 38^{\circ}\text{C}$ , Moderate:  $39$ - $39.9^{\circ}\text{C}$ , Severe:  $\geq 40^{\circ}\text{C}$ . Parents reported the use of antipyretic medication to treat or prevent symptoms in 11% and 13% of subjects aged 2 through 5 years, 9% and 10% of subjects aged 6 through 10 years for MENVEO and MENACTRA, respectively.

<sup>e</sup> Different systemic reactions were solicited in different age groups.

**Table 4. Rates of Solicited Adverse Reactions within 7 Days following Vaccination in Individuals Aged 11 through 18 Years**

Adverse Reactions	MENVEO n = 1,631 %			MENACTRA n = 539 %		
	Any	Moderate	Severe	Any	Moderate	Severe
<b>Local Adverse Reactions</b>						
Injection site pain <sup>a</sup>	44	9	1	53	11	1
Erythema <sup>b</sup>	15	2	0.4	16	1	0
Induration <sup>b</sup>	12	2	0.2	11	1	0
<b>Systemic Adverse Reactions</b>						
Headache <sup>a</sup>	29	8	2	28	7	1
Myalgia <sup>a</sup>	19	4	1	18	5	0.4
Nausea <sup>a</sup>	12	3	1	9	2	1
Malaise <sup>a</sup>	11	3	1	12	5	1
Chills <sup>a</sup>	8	2	1	7	1	0.2
Arthralgia <sup>a</sup>	8	2	0.4	6	1	0
Rash <sup>c</sup>	3	-	-	3	-	-
Fever <sup>d</sup>	1	0.4	0	1	0	0

Clinicaltrials.gov Identifier NCT00450437.<sup>12</sup>

<sup>a</sup> Moderate: Some limitation in normal daily activity, Severe: Unable to perform normal daily activity.

<sup>b</sup> Moderate:  $\geq 50$ -100 mm, Severe:  $> 100$  mm.

<sup>c</sup> Rash was assessed only as present or not present, without a grading for severity.

<sup>d</sup> Fever grading: Any:  $\geq 38^{\circ}\text{C}$ , Moderate:  $39$ - $39.9^{\circ}\text{C}$ , Severe:  $\geq 40^{\circ}\text{C}$ .

**Table 5. Rates of Solicited Adverse Reactions within 7 Days following Vaccination in Individuals Aged 19 through 55 Years**

Adverse Reactions	MENVEO n = 1,018 %			MENACTRA n = 336 %		
	Any	Moderate	Severe	Any	Moderate	Severe
<b>Local Adverse Reactions</b>						
Injection site pain <sup>a</sup>	38	7	0.3	41	6	0
Erythema <sup>b</sup>	16	2	1	12	1	0
Induration <sup>b</sup>	13	1	0.4	9	0.3	0
<b>Systemic Adverse Reactions</b>						
Headache <sup>a</sup>	25	7	2	25	7	1
Myalgia <sup>a</sup>	14	4	0.5	15	3	1

Malaise <sup>a</sup>	10	3	1	10	2	1
Nausea <sup>a</sup>	7	2	0.4	5	1	0.3
Arthralgia <sup>a</sup>	6	2	0.4	6	1	1
Chills <sup>a</sup>	4	1	0.1	4	1	0
Rash <sup>c</sup>	2	-	-	1	-	-
Fever <sup>d</sup>	1	0.3	0	1	0.3	0

Clinicaltrials.gov Identifier NCT00450437.<sup>12</sup>

<sup>a</sup> Moderate: Some limitation in normal daily activity, Severe: Unable to perform normal daily activity.

<sup>b</sup> Moderate:  $\geq 50$ -100 mm, Severe:  $> 100$  mm.

<sup>c</sup> Rash was assessed only as present or not present, without a grading for severity.

<sup>d</sup> Fever grading: Any:  $\geq 38^{\circ}\text{C}$ , Moderate:  $39$ - $39.9^{\circ}\text{C}$ , Severe:  $\geq 40^{\circ}\text{C}$ .

#### Solicited Adverse Reactions in the Booster Vaccination Study (Adolescents and Adults)

A multicenter, open-label clinical trial (NCT02986854)<sup>15</sup> was conducted in the U.S. in subjects aged 15 through 55 years [see *Clinical Studies (14.2)*]. The methodology for evaluating solicited adverse reactions, unsolicited adverse events, and serious adverse events after a booster dose of MENVEO was similar to the primary vaccination studies. The most common solicited local and systemic adverse reactions within 7 days of vaccination were pain at injection site (36%) and fatigue (38%), respectively.

#### Solicited Adverse Reactions following Concomitant Vaccine Administration

The safety of 4-dose series of MENVEO administered concomitantly with U.S.-licensed routine infant and toddler vaccines was evaluated in one pivotal trial<sup>2</sup>. The safety of a 2-dose series of MENVEO initiated at 7-9 months of age, with the second dose administered concomitantly with U.S.-licensed MMR and V vaccine at 12 months of age, was evaluated in one pivotal trial.<sup>5</sup> Rates of solicited adverse reactions which occurred 7 days following vaccination are shown in Tables 1 and 2, respectively. There was no significant increase in the rates of solicited systemic or local reactions observed in recipients of routine childhood vaccines when concomitantly vaccinated with MENVEO. [See *Drug Interactions (7.1)*.]

The safety of MENVEO administered concomitantly with Tdap and HPV was evaluated in a single-center study<sup>14</sup> conducted in Costa Rica. Solicited local and systemic adverse reactions were reported as noted above. In this study, subjects aged 11 through 18 years received MENVEO concomitantly with Tdap and HPV (n = 540), or MENVEO followed 1 month later by Tdap and then 1 month later by HPV (n = 541), or Tdap followed 1 month later by MENVEO and then 1 month later by HPV (n = 539). Some solicited systemic adverse reactions were more frequently reported in the group that received MENVEO, Tdap, and HPV concomitantly, (headache 40%, malaise 25%, myalgia 27%, and arthralgia 17%) compared with the group that first received MENVEO alone (headache 36%, malaise 20%, myalgia 19%, and arthralgia 11%). Among subjects administered MENVEO alone (1 month prior to Tdap), 36% reported headache,

20% malaise, and 16% myalgia. Among subjects administered MENVEO 1 month after Tdap, 27% reported headache, 18% malaise, and 16% myalgia.

#### Serious Adverse Events in All Safety Studies

Serious adverse events in subjects receiving a 4-dose series of MENVEO at 2, 4, 6, and 12 months were evaluated in 3 randomized, multicenter clinical studies.<sup>1-3</sup> In the 2 controlled studies,<sup>2,3</sup> the proportions of infants randomized to receive the 4-dose series of MENVEO concomitantly with routine vaccinations and infants who received routine vaccinations alone that reported serious adverse events during different study periods were, respectively: a) 2.7% and 2.2% during the infant series, b) 2.5% and 2.5% between the infant series and the toddler dose, c) 0.3% and 0.3% in the 1 month following the toddler dose, and d) 1.6% and 2.2% during the 6-month follow-up period after the last dose. In the third study,<sup>1</sup> which was controlled up to the toddler dose, the proportions of infants randomized to dosing regimens that included receiving 4 doses of MENVEO concomitantly with routine vaccinations at 2, 4, 6, and 12 months and infants who received routine vaccinations alone that reported serious adverse events during different study periods were, respectively: a) 3.5% and 3.6% during the infant series, and b) 2.8% and 3.3% between the infant series and the toddler dose, and c) 0.5% and 0.7% in the 1 month following the toddler dose. In the same study, 1.9% of infants randomized to receive the 4-dose series of MENVEO concomitantly with routine vaccinations reported serious adverse events during the 6-month follow-up period after the toddler dose. The most common serious adverse events reported in these 3 studies were wheezing, pneumonia, gastroenteritis, and convulsions, and most occurred at highest frequency after the infant series.

In a study of older infants<sup>5</sup> randomized to receive the 2-dose series of MENVEO concomitantly with MMRV at 12 months of age, the rates of serious adverse events during the study, including the 6-month follow-up period after the last dose, were 3.6% and 3.8% for the groups receiving MENVEO with MMRV and MENVEO only, respectively. Infants receiving MMRV alone, who had a shorter period of study participation as they were enrolled at 12 months of age, had a lower rate of serious adverse events (1.5%). Among 1,597 study subjects included in the safety population, the most commonly reported serious adverse events in all study arms combined were dehydration (0.4%) and gastroenteritis (0.3%). Across the submitted studies of individuals aged 2 through 23 months within 28 days of vaccination, 2 deaths were reported in the groups receiving MENVEO (one case of sudden death and one case of sepsis), while no deaths were reported in the control group. None of the deaths was assessed as related to vaccination. Among subjects with symptom onset within 42 days of vaccination (Days 12, 25, 29), 3/12,049 (0.02%, 95% CI: [0.01%, 0.07%]) recipients of MENVEO and 0/2,877 (0%, 95% CI: [0%, 0.13%]) control recipients were diagnosed with Kawasaki Disease. One case of acute disseminated encephalomyelitis with symptom onset 29 days post Dose 4 was observed in a participant given MENVEO coadministered with routine U.S. childhood vaccines at 12 months of age (including MMR and varicella vaccines).

The information regarding serious adverse events in subjects aged 2 through 10 years was derived from 3 randomized, controlled clinical trials.<sup>7-9</sup> Safety follow-up ranged from 6 through 12 months and included 2,883 subjects administered MENVEO. Serious adverse events reported during the safety follow-up periods occurred in 21/2,883 (0.7%) subjects receiving MENVEO, in 7/1,255 (0.6%) MENACTRA subjects, and 2/861 (0.2%) MENOMUNE subjects. In the subjects receiving either 1 or 2 doses of MENVEO, there were 6 subjects with pneumonia, 3 subjects with appendicitis, and 2 subjects with dehydration; all other events were reported to occur in one subject. Among 1,255 subjects administered a single dose of MENACTRA and 861 subjects administered MENOMUNE, there were no events reported to occur in more than 1 subject. The serious adverse events occurring within the first 30 days after receipt of each vaccine were as follows: MENVEO (6/2,883 [0.2%]) — appendicitis, pneumonia, staphylococcal infection, dehydration, febrile convulsion, and tonic convulsion; MENACTRA (1/1255 [0.1%]) — inguinal hernia; MENOMUNE (2/861 [0.2%]) — abdominal pain, lobar pneumonia. In a supportive study,<sup>6</sup> 298 subjects received 1 or 2 doses of MENVEO and 22 (7%) had serious adverse events over a 13-month follow-up period including 13 subjects with varicella and 2 subjects with laryngitis. All other events were reported to occur in 1 subject. During the 30 days post vaccination in this study, 1 limb injury and 1 case of varicella were reported.

The information regarding serious adverse events in subjects aged 11 through 55 years was derived from 5 randomized, controlled clinical trials.<sup>10-14</sup> Serious adverse events reported within 6 months of vaccination occurred in 40/6,185 (0.6%) subjects receiving MENVEO, 13/1,757 (0.7%) MENACTRA subjects, and 5/209 (2.4%) MENOMUNE subjects. During the 6 months following immunization, serious adverse events reported by more than 1 subject were as follows: MENVEO - appendicitis (3 subjects), road traffic accident (3 subjects), and suicide attempt (5 subjects); MENACTRA - intervertebral disc protrusion (2 subjects); MENOMUNE - none. Serious adverse events that occurred within 30 days of vaccination were reported by 7 of 6,185 (0.1%) subjects in the group receiving MENVEO, 4 of 1,757 (0.2%) subjects in the MENACTRA group, and by none of 209 subjects in the MENOMUNE group. The events that occurred during the first 30 days post immunization with MENVEO were: vitello-intestinal duct remnant, Cushing's syndrome, viral hepatitis, pelvic inflammatory disease, intentional multiple-drug overdose, simple partial seizure, and suicidal depression. The events that occurred during the first 30 days post immunization with MENACTRA were: herpes zoster, fall, intervertebral disc protrusion, and angioedema.

## **6.2 Postmarketing Experience**

In addition to reports in clinical trials, the following adverse reactions have been identified during postapproval use of MENVEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Ear and Labyrinth Disorders

Hearing impaired, ear pain, vertigo, vestibular disorder.

Eye Disorders

Eyelid ptosis.

General Disorders and Administration Site Conditions

Injection site pruritus; pain; erythema; inflammation; and swelling, including extensive swelling of the vaccinated limb; fatigue; malaise; pyrexia.

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

Infections and Infestations

Vaccination site cellulitis.

Injury, Poisoning, and Procedural Complications

Fall, head injury.

Investigation

Alanine aminotransferase increased, body temperature increased.

Musculoskeletal and Connective Tissue Disorders

Arthralgia, bone pain.

Nervous System Disorders

Dizziness, syncope, tonic convulsion, headache, facial paresis, balance disorder.

Respiratory, Thoracic, and Mediastinal Disorders

Oropharyngeal pain.

Skin and Subcutaneous Tissue Disorders

Skin exfoliation.

Postmarketing Observational Safety Study

In a postmarketing observational safety study conducted in a U.S. health maintenance organization, data from electronic health records of 48,899 persons aged 11 through 21 years were used to evaluate pre-specified events of interest following vaccination with MENVEO. Using a self-controlled case series method, Bell's palsy showed a statistically significant increased risk in the period 1 to 84 days post vaccination compared with the control period, with an overall adjusted relative incidence of 2.9 (95% CI: 1.1-7.5). Among the 8 reported cases of Bell's palsy, 6 cases occurred in persons who received MENVEO concomitantly with one or



more of the following vaccines: Tdap, HPV, and Influenza vaccine. All reported Bell's palsy cases resolved.

## **7 DRUG INTERACTIONS**

### **7.1 Concomitant Administration with Other Vaccines**

Do not mix MENVEO or any of its components with any other vaccine or diluent in the same syringe or vial.

In 2 clinical trials of infants initiating vaccination at 2 months of age,<sup>1,3</sup> MENVEO was given concomitantly at 2, 4, and 6 months with routine infant vaccines: diphtheria toxoid; acellular pertussis; tetanus toxoid; inactivated polio types 1, 2, and 3; hepatitis B; *Haemophilus influenzae* type b (Hib) antigens; pentavalent rotavirus; and 7-valent pneumococcal conjugate vaccine. For Dose 4 given at 12 months of age, MENVEO was given concomitantly with the following vaccines: 7-valent pneumococcal conjugate, MMRV, or MMR+V, and inactivated hepatitis A. In a clinical trial of older infants (aged 7 months and older) and toddlers,<sup>5</sup> MENVEO was administered concomitantly with MMRV or MMR+V vaccine(s) at 12 months of age. No immune interference was observed for the concomitantly administered vaccines, including most pneumococcal vaccine serotypes (post Dose 3); no immune interference was observed post Dose 4 for any pneumococcal vaccine serotypes.<sup>1,3</sup> [See *Clinical Studies* (14.3).]

For children aged 2 through 10 years, no data are available to evaluate safety and immunogenicity of other childhood vaccines when administered concomitantly with MENVEO.

In a clinical trial in adolescents,<sup>14</sup> MENVEO was given concomitantly with the following: Tdap and HPV; no interference was observed in meningococcal immune responses when compared with MENVEO given alone. Lower geometric mean antibody concentrations (GMCs) for antibodies to the pertussis antigens filamentous hemagglutinin (FHA) and pertactin were observed when MENVEO was administered concomitantly with Tdap and HPV as compared with Tdap alone. [See *Clinical Studies* (14.3).]

### **7.2 Immunosuppressive Treatments**

Immunosuppressive therapies, such as irradiation, antimetabolite medications, alkylating agents, cytotoxic drugs, and corticosteroids (when used in greater than physiologic doses) may reduce the immune response to MENVEO [see *Warnings and Precautions* (5.3)]. The immunogenicity of MENVEO has not been evaluated in persons receiving such therapies.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are no adequate and well-controlled studies of MENVEO in pregnant women in the U.S. There was a pregnancy exposure registry conducted from 2014-2017 that included 82 subjects. Available data do not suggest an increased risk of major birth defects and miscarriage in women who received MENVEO within 28 days prior to conception or during pregnancy (*see Data*).

A developmental toxicity study was performed in female rabbits administered 0.5 mL (at each occasion) of MENVEO prior to mating and during gestation. A single human dose is 0.5 mL. This study revealed no adverse effects on fetal or pre-weaning development (*see Data*).

#### Data

*Human Data:* A pregnancy exposure registry (2014 to 2017) included 82 pregnancies with known outcomes with exposure within 28 days prior to conception or during pregnancy. Miscarriage was reported for 12.2% of pregnancies with exposure to MENVEO within 28 days prior to conception or during pregnancy (10/82). Major birth defects were reported for 3.6% of live born infants whose mothers were exposed within 28 days prior to conception or during pregnancy (2/55). The rates of miscarriage and major birth defects were consistent with estimated background rates.

*Animal Data:* In a developmental toxicity study, female rabbits were administered MENVEO by intramuscular injection on Days 29, 15, and 1 prior to mating and on Gestation Days 7 and 20. The total dose was 0.5 mL at each occasion (a single human dose is 0.5 mL). No adverse effects on pre-weaning development up to Postnatal Day 29 were observed. There were no vaccine-related fetal malformations or variations observed.

### **8.2 Lactation**

#### Risk Summary

It is not known whether the vaccine components of MENVEO are excreted in human milk. Data are not available to assess the effects of MENVEO in the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MENVEO and any potential adverse effects on the breastfed child from MENVEO or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

#### **8.4 Pediatric Populations**

Safety and effectiveness of MENVEO in children aged younger than 2 months have not been established.

#### **8.5 Geriatric Populations**

Safety and effectiveness of MENVEO in adults aged 65 years and older have not been established.

### **11 DESCRIPTION**

MENVEO [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM<sub>197</sub> Conjugate Vaccine] is a sterile liquid vaccine administered by intramuscular injection that contains *N. meningitidis* serogroup A, C, Y, and W-135 oligosaccharides conjugated individually to *Corynebacterium diphtheriae* CRM<sub>197</sub> protein. The polysaccharides are produced by bacterial fermentation of *N. meningitidis* (serogroups A, C, Y, or W-135). *N. meningitidis* strains A, C, Y, and W-135 are each cultured and grown on Franz Complete medium and treated with formaldehyde. MenA, MenW-135, and MenY polysaccharides are purified by several extraction and precipitation steps. MenC polysaccharide is purified by a combination of chromatography and precipitation steps.

The protein carrier (CRM<sub>197</sub>) is produced by bacterial fermentation and is purified by a series of chromatography and ultrafiltration steps. *C. diphtheriae* is cultured and grown on CY medium containing yeast extracts and amino acids.

The oligosaccharides are prepared for conjugation from purified polysaccharides by hydrolysis, sizing, and reductive amination. After activation, each oligosaccharide is covalently linked to the CRM<sub>197</sub> protein. The resulting glycoconjugates are purified to yield the 4 drug substances, which compose the final vaccine. The vaccine contains no preservative or adjuvant. Each dose of vaccine contains 10 mcg MenA oligosaccharide; 5 mcg of each of MenC, MenY, and MenW-135 oligosaccharides; and 32.7 to 64.1 mcg CRM<sub>197</sub> protein. Residual formaldehyde per dose is estimated to be not more than 0.30 mcg.

The vials in which the vaccine components are contained are composed of Type I glass, USP.

The container closures (synthetic rubber stoppers) are not made with natural rubber latex.

### **12 CLINICAL PHARMACOLOGY**

#### **12.1 Mechanism of Action**

*Neisseria meningitidis* is a gram-negative diplococcus that causes life-threatening invasive disease such as meningitis and sepsis. Globally, 5 serogroups, A, B, C, Y, and W-135 cause almost all invasive meningococcal infections. The presence of serum bactericidal antibodies protects against invasive meningococcal disease.<sup>16</sup> Vaccination with MENVEO leads to the

production of bactericidal antibodies directed against the capsular polysaccharides of serogroups A, C, Y, and W-135.

### **13 NONCLINICAL TOXICOLOGY**

#### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

MENVEO has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals. Vaccination of female rabbits with MENVEO had no effect on fertility. *[See Use in Specific Populations (8.1).]*

### **14 CLINICAL STUDIES**

For all age groups, effectiveness has been inferred from the measurement of serogroup-specific anticapsular antibodies with bactericidal activity using pooled human serum that lacked bactericidal activity as the source of exogenous complement (hSBA).

#### **14.1 Primary Vaccination Studies**

In the absence of a licensed comparator vaccine for use in infants, the pre-specified endpoint for effectiveness of MENVEO in U.S. infants receiving a 4-dose series at 2, 4, 6, and 12 months of age was the proportion of subjects achieving an hSBA  $\geq 1:8$ , with the lower limit of the 2-sided 95% CI for the point estimate being  $\geq 80\%$  of vaccinees for serogroup A, and  $\geq 85\%$  of vaccinees for serogroups C, W-135, and Y 1 month following the final dose.

The effectiveness of MENVEO in subjects aged 2 through 55 years was assessed by comparing the hSBA responses to immunization with MENVEO to those following immunization with the licensed meningococcal quadrivalent conjugate vaccine MENACTRA.

The primary effectiveness endpoint was hSBA seroresponse to each serogroup 28 days after vaccination. Seroresponse was defined as: a) post-vaccination hSBA  $\geq 1:8$  for subjects with a baseline hSBA  $< 1:4$ ; or, b) at least 4-fold higher than baseline titers for subjects with a pre-vaccination hSBA  $\geq 1:4$ . Secondary endpoints included the proportion of subjects with post-vaccination hSBA  $\geq 1:8$  and the hSBA Geometric Mean Titer (GMT) for each serogroup. In a separate group of children aged 2 through 5 years randomized to receive 2 doses of MENVEO administered 2 months apart, seroresponse rate, proportion with post-vaccination hSBA  $\geq 1:8$ , and GMT were determined for each serogroup.

#### Immunogenicity in Infants/Toddlers Aged 2 Months through 12 Months

The effectiveness of MENVEO in infants was assessed in a randomized, controlled, multicenter study.<sup>3</sup> Among the subjects receiving MENVEO who were included in the per-protocol analysis, the mean age at enrollment was 65 days, 51% were male, 67% were Caucasian, 6% were African American, 15% were Hispanic, 2% were Asian, and 9% were noted as other racial/ethnic groups. The pre-defined criteria for immunogenicity were met for all 4 serogroups A, C, W-135, and Y at 1 month following completion of a 4-dose series at 2, 4, 6, and 12 months of age (Table 6).

The percentage of subjects with hSBA  $\geq 1:8$  at 7 months was 94% to 98% for serogroups C, W-135, and Y and 76% for serogroup A.

**Table 6. Bactericidal Antibody Responses following Administration of MENVEO with Routine Infant/Toddler Vaccines at 2, 4, 6, and 12 Months of Age**

Serogroup		Post 3 <sup>rd</sup> Dose	Post 4 <sup>th</sup> Dose
A		<b>n = 202</b>	<b>n = 168</b>
	% $\geq 1:8$	76	89
	95% CI	(69, 81)	(83 <sup>a</sup> , 93)
	GMT	21	54
C		<b>n = 199</b>	<b>n = 156</b>
	% $\geq 1:8$	94	95
	95% CI	(90, 97)	(90 <sup>a</sup> , 98)
	GMT	74	135
W-135		<b>n = 194</b>	<b>n = 153</b>
	% $\geq 1:8$	98	97
	95% CI	(95, 99)	(93 <sup>a</sup> , 99)
	GMT	79	215
Y		<b>n = 188</b>	<b>n = 153</b>
	% $\geq 1:8$	94	96
	95% CI	(89, 97)	(92 <sup>a</sup> , 99)
	GMT	51	185
	95% CI	(43, 61)	(148, 233)

Clinicaltrials.gov Identifier NCT01000311.<sup>3</sup>

%  $\geq 1:8$  = Proportions of subjects with hSBA  $\geq 1:8$  against a given serogroup; CI = Confidence interval; GMT = Geometric mean antibody titer; n = Number of infants eligible for inclusion in the Per-Protocol Immunogenicity population for whom serological results were available for the post-Dose 3 and post-Dose 4 evaluations.

Serum Bactericidal Assay with exogenous human complement source (hSBA).

<sup>a</sup> Pre-specified criteria for adequacy of immune response were met (lower limit of the 95% CI  $>80\%$  for serogroup A and  $>85\%$  for serogroups C, W, and Y).

The effectiveness of 2 doses of MENVEO given at 7-9 months and 12 months of age was assessed in a randomized, multicenter, controlled clinical trial<sup>5</sup> conducted in the U.S. This study also investigated the concomitant administration of MENVEO and MMRV. The per-protocol population for assessing the response to 2 doses of MENVEO consisted of 386 subjects. Among subjects who completed the per-protocol analysis, their mean age at enrollment was 8.5 months

(SD: 0.8 months), 50% were male; 61% were Caucasian, 15% were Hispanic, 10% were African American, 4% were Asian, and 10% were noted as other racial/ethnic groups.

Among the per-protocol population, after MENVEO administered at 7-9 and at 12 months, the proportions of subjects with hSBA  $\geq 1:8$  for serogroups A, C, W-135, and Y were respectively: 88% (84-91), 100% (98-100), 98% (96-100), 96% (93-99).

#### Immunogenicity in Children Aged 2 Years through 10 Years

Effectiveness in subjects aged 2 through 10 years was evaluated in a randomized, multicenter, active-controlled clinical study<sup>9</sup> comparing hSBA responses following 1 dose of MENVEO or MENACTRA. The study was conducted in the U.S. and Canada and was stratified by age (2 through 5 years and 6 through 10 years). The per-protocol population evaluated after a single dose of vaccine consisted of 1,170 subjects who received MENVEO and 1,161 who received MENACTRA (Table 7) and included serological results for 89% to 95% of subjects, depending on serogroup and age group. Demographics for the 616 and 619 subjects aged 2 through 5 years for MENVEO and MENACTRA were as follows: mean age 3.6 years (SD: 1.1) vs. 3.6 years (SD: 1.1), 51% vs. 52% male, 62% vs. 62% Caucasian, 14% vs. 13% Hispanic, 12% vs. 13% African American, 6% vs. 4% Asian, and 7% vs. 8% other racial/ethnic groups, respectively. Demographics were for 554 and 542 per-protocol subjects aged 6 through 10 years for MENVEO and MENACTRA were as follows: mean age 7.9 years (SD: 1.4) vs. 8.1 years (SD: 1.4), 52% vs. 56% male, 66% vs. 66% Caucasian, 14% vs. 14% African American, 7% vs. 7% Hispanic, 5% vs. 6% Asian, and 8% vs. 8% other racial/ethnic groups, respectively. In a separate group of children aged 2 through 5 years randomized to receive 2 doses of MENVEO administered 2 months apart, the per-protocol population evaluated after 2 doses of MENVEO consisted of 297 subjects and included serologic results for 96% to 99% of subjects, depending on serogroup.

In study participants aged 2 through 5 years and 6 through 10 years, non-inferiority of MENVEO to MENACTRA for the proportion of subjects with a seroresponse was demonstrated for serogroups C, W-135, and Y, but not for serogroup A (Table 7).

**Table 7. Comparison of Bactericidal Antibody Responses<sup>a</sup> to MENVEO and MENACTRA  
28 Days after Vaccination of Subjects Aged 2 through 5 Years and 6 through 10 Years**

Endpoint by Serogroup	2-5 Years			6-10 Years		
	MENVEO (95% CI)	MENACTRA (95% CI)	Percent Difference (MENVEO – MENACTRA) or GMT Ratio (MENVEO/ MENACTRA) (95% CI)	MENVEO (95% CI)	MENACTRA (95% CI)	Percent Difference (MENVEO – MENACTRA) or GMT Ratio (MENVEO/ MENACTRA) (95% CI)
<b>A</b>	<b>n = 606</b>	<b>n = 611</b>		<b>n = 551</b>	<b>n = 541</b>	
% Seroresponse <sup>b</sup>	72 (68, 75)	77 (73, 80)	-5 (-10, -0) <sup>c</sup>	77 (73, 80)	83 (79, 86)	-6 (-11, -1) <sup>c</sup>
% ≥1:8	72 (68, 75)	78 (74, 81)	-6 (-11, -1)	77 (74, 81)	83 (80, 86)	-6 (-11, -1)
GMT	26 (22, 30)	25 (21, 29)	1.04 (0.86, 1.27)	35 (29, 42)	35 (29, 41)	1.01 (0.83, 1.24)
<b>C</b>	<b>n = 607</b>	<b>n = 615</b>		<b>n = 554</b>	<b>n = 539</b>	
% Seroresponse <sup>b</sup>	60 (56, 64)	56 (52, 60)	4 (-2, 9) <sup>d</sup>	63 (59, 67)	57 (53, 62)	6 (0, 11) <sup>d</sup>
% ≥1:8	68 (64, 72)	64 (60, 68)	4 (-1, 10)	77 (73, 80)	74 (70, 77)	3 (-2, 8)
GMT	18 (15, 20)	13 (11, 15)	1.33 (1.11, 1.6)	36 (29, 45)	27 (21, 33)	1.36 (1.06, 1.73)
<b>W-135</b>	<b>n = 594</b>	<b>n = 605</b>		<b>n = 542</b>	<b>n = 533</b>	
% Seroresponse <sup>b</sup>	72 (68, 75)	58 (54, 62)	14 (9, 19) <sup>d</sup>	57 (53, 61)	44 (40, 49)	13 (7, 18) <sup>d</sup>
% ≥1:8	90 (87, 92)	75 (71, 78)	15 (11, 19)	91 (88, 93)	84 (81, 87)	7 (3, 11)
GMT	43 (38, 50)	21 (19, 25)	2.02 (1.71, 2.39)	61 (52, 72)	35 (30, 42)	1.72 (1.44, 2.06)
<b>Y</b>	<b>n = 593</b>	<b>n = 600</b>		<b>n = 545</b>	<b>n = 539</b>	
% Seroresponse <sup>b</sup>	66 (62, 70)	45 (41, 49)	21 (16, 27) <sup>d</sup>	58 (54, 62)	39 (35, 44)	19 (13, 24) <sup>d</sup>
% ≥1:8	76 (72, 79)	57 (53, 61)	19 (14, 24)	79 (76, 83)	63 (59, 67)	16 (11, 21)
GMT	24 (20, 28)	10 (8.68, 12)	2.36 (1.95, 2.85)	34 (28, 41)	14 (12, 17)	2.41 (1.95, 2.97)

Clinicaltrials.gov Identifier NCT00616421.<sup>9</sup>

<sup>a</sup> Serum Bactericidal Assay with exogenous human complement source (hSBA).



- <sup>b</sup> Seroresponse was defined as: Subjects with a pre-vaccination hSBA <1:4, a post-vaccination titer of >1:8 and among subjects with a pre-vaccination hSBA  $\geq$ 1:4, a post-vaccination titer at least 4-fold higher than baseline.
- <sup>c</sup> Non-inferiority criterion not met (the lower limit of the 2-sided 95% CI  $\leq$ -10% for vaccine group differences).
- <sup>d</sup> Non-inferiority criterion met (the lower limit of the 2-sided 95% CI  $>$ -10% for vaccine group differences [MENVEO minus MENACTRA]).

In the 297 per-protocol subjects aged 2 through 5 years observed at 1 month after the second dose of MENVEO, the proportions of subjects with seroresponse (95% CI) were: 91% (87-94), 98% (95-99), 89% (85-92), and 95% (91-97) for serogroups A, C, W-135, and Y, respectively. The proportion of subjects with hSBA  $\geq$ 1:8 (95% CI) were 91% (88-94), 99% (97-100), 99% (98-100), and 98% (95-99) for serogroups A, C, W-135, and Y, respectively. The hSBA GMTs (95% CI) for this group were 64 (51-81), 144 (118-177), 132 (111-157), and 102 (82-126) for serogroups A, C, W-135, and Y, respectively.

#### Immunogenicity in Adolescents Aged 11 Years through 18 Years

Effectiveness in subjects aged 11 through 55 years was evaluated in a randomized, multicenter, active-controlled clinical study<sup>12</sup> comparing the hSBA responses following 1 dose of MENVEO or MENACTRA. The study was conducted in the U.S. and stratified by age (11 through 18 years and 19 through 55 years). This study enrolled 3,539 participants, who were randomized to receive a dose of MENVEO (n = 2,663) or MENACTRA (n = 876). Among subjects who completed the per-protocol evaluation for immunogenicity (n = 3,393, MENVEO = 2,549, MENACTRA = 844), demographics for subjects receiving MENVEO and MENACTRA, respectively, were as follows: mean age 23.9 (SD: 13.6) vs. 23.7 (SD: 13.7), 42% vs. 42% male, 79% vs. 78% Caucasian, 8% vs. 9% African American, 7% vs. 7% Hispanic, 3% vs. 3% Asian, 2% vs. 3% other racial/ethnic groups. Immunogenicity for each serogroup was assessed in a subset of study participants (Tables 8 and 9).

In study participants aged 11 through 18 years, non-inferiority of MENVEO to MENACTRA was demonstrated for all 4 serogroups for the proportion of subjects with a seroresponse (Table 8).

**Table 8. Comparison of Bactericidal Antibody Responses<sup>a</sup> to MENVEO and MENACTRA 28 Days after Vaccination of Subjects Aged 11 through 18 Years**

Endpoint by Serogroup	Bactericidal Antibody Response <sup>a</sup>		Comparison of MENVEO and MENACTRA	
	MENVEO (95% CI)	MENACTRA (95% CI)	MENVEO/ MENACTRA (95% CI)	MENVEO minus MENACTRA (95% CI)
<b>A</b>	<b>n = 1,075</b>	<b>n = 359</b>		
% Seroresponse <sup>b</sup>	75 (72, 77)	66 (61, 71)		8 (3, 14) <sup>c</sup>
% $\geq 1:8$	75 (73, 78)	67 (62, 72)	-	8 (3, 14)
GMT	29 (24, 35)	18 (14, 23)	1.63 (1.31, 2.02)	-
<b>C</b>	<b>n = 1,396</b>	<b>n = 460</b>		
% Seroresponse <sup>b</sup>	76 (73, 78)	73 (69, 77)		2 (-2, 7) <sup>c</sup>
% $\geq 1:8$	85 (83, 87)	85 (81, 88)	-	0 (-4, 4)
GMT	50 (39, 65)	41 (30, 55)	1.22 (0.97, 1.55)	-
<b>W-135</b>	<b>n = 1,024</b>	<b>n = 288</b>		
% Seroresponse <sup>b</sup>	75 (72, 77)	63 (57, 68)		12 (6, 18) <sup>c</sup>
% $\geq 1:8$	96 (95, 97)	88 (84, 92)	-	8 (4, 12)
GMT	87 (74, 102)	44 (35, 54)	2.00 (1.66, 2.42)	-
<b>Y</b>	<b>n = 1,036</b>	<b>n = 294</b>		
% Seroresponse <sup>b</sup>	68 (65, 71)	41 (35, 47)		27 (20, 33) <sup>c</sup>
% $\geq 1:8$	88 (85, 90)	69 (63, 74)	-	19 (14, 25)
GMT	51 (42, 61)	18 (14, 23)	2.82 (2.26, 3.52)	-

Clinicaltrials.gov Identifier NCT00450437.<sup>12</sup><sup>a</sup> Serum Bactericidal Assay with exogenous human complement source (hSBA).

<sup>b</sup> Seroresponse was defined as: a) post-vaccination hSBA  $\geq 1:8$  for subjects with a pre-vaccination hSBA  $< 1:4$ ; or, b) at least 4-fold higher than baseline titers for subjects with a pre-vaccination hSBA  $\geq 1:4$ .

<sup>c</sup> Non-inferiority criterion for the primary endpoint met (the lower limit of the 2-sided 95% CI  $> -10\%$  for vaccine group differences [MENVEO minus MENACTRA]).

#### Immunogenicity in Adults Aged 19 Years through 55 Years

The study in subjects aged 11 through 55 years was a randomized, multicenter, active-controlled clinical trial<sup>12</sup> conducted in the U.S. and stratified by age (11 through 18 years and 19 through 55 years) as described above.

In study participants aged 19 through 55 years, non-inferiority of MENVEO to MENACTRA was demonstrated for all 4 serogroups for the proportion of subjects with a seroresponse (Table 9).

**Table 9. Comparison of Bactericidal Antibody Responses to MENVEO and MENACTRA 28 Days after Vaccination of Subjects Aged 19 through 55 Years**

Endpoint by Serogroup	Bactericidal Antibody Response <sup>a</sup>		Comparison of MENVEO and MENACTRA	
	MENVEO (95% CI)	MENACTRA (95% CI)	MENVEO/MENACTRA (95% CI)	MENVEO minus MENACTRA (95% CI)
<b>A</b>	<b>n = 963</b>	<b>n = 321</b>		
% Seroresponse <sup>b</sup>	67 (64, 70)	68 (63, 73)		-1 (-7, 5) <sup>c</sup>
% $\geq 1:8$	69 (66, 72)	71 (65, 76)	-	-2 (-7, 4)
GMT	31 (27, 36)	30 (24, 37)	1.06 (0.82, 1.37)	-
<b>C</b>	<b>n = 902</b>	<b>n = 300</b>		
% Seroresponse <sup>b</sup>	68 (64, 71)	60 (54, 65)		8 (2, 14) <sup>c</sup>
% $\geq 1:8$	80 (77, 83)	74 (69, 79)	-	6 (1, 12)
GMT	50 (43, 59)	34 (26, 43)	1.50 (1.14, 1.97)	-
<b>W-135</b>	<b>n = 484</b>	<b>n = 292</b>		
% Seroresponse <sup>b</sup>	50 (46, 55)	41 (35, 47)		9 (2, 17) <sup>c</sup>
% $\geq 1:8$	94 (91, 96)	90 (86, 93)	-	4 (0, 9)

GMT	111 (93, 132)	69 (55, 85)	1.61 (1.24, 2.1)	-
<b>Y</b>	<b>n = 503</b>	<b>n = 306</b>		
% Seroresponse <sup>b</sup>	56 (51, 60)	40 (34, 46)		16 (9, 23) <sup>c</sup>
% $\geq 1:8$	79 (76, 83)	70 (65, 75)	-	9 (3, 15)
GMT	44 (37, 52)	21 (17, 26)	2.10 (1.60, 2.75)	-

Clinicaltrials.gov Identifier NCT00450437.<sup>12</sup>

<sup>a</sup> Serum Bactericidal Assay with exogenous human complement source (hSBA).

<sup>b</sup> Seroresponse was defined as: a) post-vaccination hSBA  $>1:8$  for subjects with a pre-vaccination hSBA  $<1:4$ ; or, b) at least 4-fold higher than baseline titers for subjects with a pre-vaccination hSBA  $\geq 1:4$ .

<sup>c</sup> Non-inferiority criterion for the primary endpoint met (the lower limit of the 2-sided 95% CI  $>-10\%$  for vaccine group differences [MENVEO minus MENACTRA]).

## 14.2 Booster Vaccination Study

### Immunogenicity in Adolescents and Adults Aged 15 Years through 55 Years

For a description of study design and number of participants, see section 6.1 Booster Vaccination Study. The co-primary immunogenicity endpoints were hSBA seroresponse to each serogroup 29 days a) following a booster vaccination with MENVEO given to subjects who received a prior dose of MENVEO, and b) following a booster vaccination with MENVEO given to subjects who received a prior dose of MENACTRA. Seroresponse was defined as: a) post-vaccination hSBA  $\geq 1:16$  for subjects with a baseline hSBA  $<1:4$  or b) at least 4-fold higher than baseline titers for subjects with a pre-vaccination hSBA  $\geq 1:4$ . Secondary endpoints included the proportions of subjects with post-vaccination hSBA  $\geq 1:8$ , the hSBA GMTs for each serogroup, and antibody titers against each serogroup 4 to 6 years after a prior dose (as measured by percentages of subjects with hSBA titers  $\geq 1:8$  and hSBA GMTs prior to booster vaccination).

Seroresponse rates at Day 29 following a booster vaccination with MENVEO were 97% for serogroup A, 95% for serogroup C, 96% for serogroup W-135, and 97% for serogroup Y, in subjects who had received a prior dose of MENVEO (n = 290). At Day 6, following a booster vaccination, seroresponse rates were 39%, 51%, 50%, and 49% for serogroups A, C, W-135, and Y, respectively, in subjects who had received a prior dose of MENVEO.

The hSBA GMTs were 13, 92, 112, and 63 for serogroups A, C, W-135, and Y at Day 6, and 210, 1160, 1395, and 1067, respectively, for the 4 serogroups at Day 29 following a booster dose of MENVEO.

Overall, similar seroresponse rates and GMTs were observed for those subjects who received a booster vaccination with MENVEO following a prior dose of MENACTRA (n = 282).

Prior to booster vaccination, the percentage of subjects with hSBA titers >1:8 for serogroups A, C, W-135, and Y were 12%, 62%, 76%, and 54% for those who received a prior dose of MENVEO 4 to 6 years earlier, and 15%, 54%, 77%, and 47% for those who received a prior dose of MENACTRA 4 to 6 years earlier. The hSBA GMTs for serogroups A, C, W-135, and Y prior to booster vaccination were 3, 16, 23, and 9 following a prior vaccination with MENVEO and 3, 11, 23, and 8 following a prior vaccination with MENACTRA.

### 14.3 Immunogenicity of Concomitantly Administered Vaccines

In U.S. infants<sup>1,3</sup> who received MENVEO concomitantly with DTaP-IPV-Hib and PCV7 at 2, 4, and 6 months of age and HBV administered according to ACIP recommendations, there was no evidence for reduced antibody response to pertussis antigens (GMC to pertussis toxin, filamentous hemagglutinin, fimbriae, and pertactin), diphtheria toxoid (antibody levels  $\geq 0.1$  IU/mL), tetanus toxoid (antibody levels  $\geq 0.1$  IU/mL), poliovirus types 1, 2, and 3 (neutralizing antibody levels  $\geq 1:8$  to each virus), *Haemophilus influenzae* type b (anti-PRP antibody  $\geq 0.15$  mcg/mL), hepatitis B (anti-hepatitis B surface antigen  $\geq 10$  mIU/mL), or most serotypes of PCV7 (antibody levels  $\geq 0.35$  mcg/mL) relative to the response in infants administered DTaP-IPV-Hib, PCV7, and HBV. The immune responses to DTaP-IPV-Hib, PCV7, and HBV were evaluated 1 month following Dose 3.<sup>1,3</sup> No interference was observed for pertussis based on GMC ratios, or for the other concomitantly administered vaccines, with the exception of pneumococcal serotype 6B<sup>1,3</sup> and 23F<sup>3</sup>, for which interference was suggested post Dose 3. No interference was observed post Dose 4 for these serotypes.<sup>1,3</sup>

There was no evidence for interference in the immune response to MMR and varicella vaccines (among initially seronegative children) in terms of percentages of children with anti-measles antibodies  $\geq 255$  mIU/mL, anti-mumps  $\geq 10$  ELISA antibody units, anti-rubella  $\geq 10$  IU/mL, and anti-varicella  $\geq 5$  gp ELISA units/mL, administered at 12 months of age<sup>5</sup> concomitantly with MENVEO relative to these vaccines administered alone. The immune responses to MMR and varicella vaccines were evaluated 6 weeks post vaccination.

For children aged 2 through 10 years, no data are available for evaluating safety and immunogenicity of other childhood vaccines when administered concomitantly with MENVEO.

For individuals aged 11 through 18 years, the effect of concomitant administration of MENVEO with Tdap and HPV was evaluated in a study<sup>14</sup> conducted in Costa Rica (see also section 6.1 for the safety results from this trial). Subjects were randomized to receive one of the following regimens at the start of the trial: MENVEO plus Tdap plus HPV (n = 540); MENVEO alone (n = 541); Tdap alone (n = 539). Subjects were healthy adolescents aged 11 through 18 years (mean age between groups was 13.8 to 13.9 years). For antigens of MENVEO, the proportion (95% CI) of subjects achieving an hSBA seroresponse among those who received MENVEO plus Tdap plus HPV vs. MENVEO alone, respectively, were: serogroup A 80% (76, 84) vs. 82% (78, 85); serogroup C 83% (80, 87) vs. 84% (80, 87); serogroup W-135 77% (73, 80) vs. 81% (77, 84); serogroup Y 83% (79, 86) vs. 82% (79, 86). Among subjects who received Tdap plus

MENVEO plus HPV, compared with Tdap alone, the proportions (95% CI) of subjects who achieved an anti-tetanus or anti-diphtheria toxoids levels  $\geq 1.0$  IU/mL in the 2 groups, respectively, were 100% (99, 100) vs. 98% (96, 99) and 100% (99, 100) vs. 100% (99, 100). For pertussis antigens, among subjects who received Tdap plus MENVEO plus HPV, compared with Tdap alone, the responses respectively for anti-pertussis toxin GMCs (95% CI) were 51 (47, 55) vs. 63 (58, 69) ELISA Units (EU)/mL, for anti-filamentous hemagglutinin were 342 (310, 376) vs. 511 (464, 563) EU/mL, and for anti-pertactin were 819 (727, 923) vs. 1,197 (1,061, 1,350) EU/mL. Because there are no established serological correlates of protection for pertussis, the clinical implications of the lower pertussis antigen responses are unknown.

## 15 REFERENCES

All NCT numbers are as noted in the National Library of Medicine clinical trial database (see [clinicaltrials.gov](https://clinicaltrials.gov)).

1. NCT00474526 (V59P14).
2. NCT00806195 (V59P23).
3. NCT01000311 (V59\_33).
4. NCT00310856 (V59P9).
5. NCT00626327 (V59P21).
6. NCT00310817 (V59P7).
7. NCT00262028 (V59P8).
8. NCT00329849 (V59P10).
9. NCT00616421 (V59P20).
10. NCT01018732 (V59P6).
11. NCT00329901 (V59P11).
12. NCT00450437 (V59P13).
13. NCT00474487 (V59P17).
14. NCT00518180 (V59P18).
15. NCT02986854 (V59\_77).
16. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. *J Exp Med.* (1969);129:1307-1326.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

MENVEO is supplied as:

- 5 Vials containing MenCYW-135 Liquid Conjugate Component (Vial 1; grey cap)
- 5 Vials containing MenA Lyophilized Conjugate Component (Vial 2; orange cap)

One vial of MenCYW-135 liquid conjugate component (Vial 1) and one vial of MenA lyophilized conjugate component (Vial 2) must be combined before use to form a single dose of MENVEO (packaged without syringes or needles). The container closures (synthetic rubber stoppers) are not made with natural rubber latex.

**Table 10. Product Presentation for MENVEO**

Presentation	Carton NDC Number	Components	
		MenCYW-135 Liquid Conjugate Component (Vial 1; grey cap)	MenA Lyophilized Conjugate Component (powder) (Vial 2; orange cap)
Carton of 5 doses (10 vials)	58160-955-09	5 Vials NDC 58160-959-01	5 Vials NDC 58160-958-01

## 16.2 Storage before Reconstitution

**Do not freeze. Frozen/previously frozen product should be discarded.**

Store refrigerated, away from the freezer compartment, at 36°F to 46°F (2°C to 8°C).

Protect from light. Vaccine must be maintained at 36°F to 46°F during transport.

Do not use after the expiration date.

## 16.3 Storage after Reconstitution

The reconstituted vaccine should be used immediately, but may be held at 36°F to 77°F (2°C to 25°C) for up to 8 hours. Do not freeze. Discard reconstituted vaccine if it has been frozen or not used within 8 hours.

## 17 PATIENT COUNSELING INFORMATION

- Give the patient, parent, or guardian the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).

Inform patients, parents, or guardians about:

- Potential benefits and risks of immunization with MENVEO.



- The importance of completing the immunization series.
- Potential for adverse reactions that have been temporally associated with administration of MENVEO or other vaccines containing similar components.
- Reporting any adverse reactions to their healthcare provider.

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MNV:5PI

# **EXHIBIT 262**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use KINRIX safely and effectively. See full prescribing information for KINRIX.

**KINRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine) Suspension for Intramuscular Injection**  
Initial U.S. Approval: 2008

**INDICATIONS AND USAGE**

A single dose of KINRIX is indicated for active immunization against diphtheria, tetanus, pertussis, and poliomyelitis as the fifth dose in the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine series and the fourth dose in the inactivated poliovirus vaccine (IPV) series in children aged 4 through 6 years (prior to the 7th birthday) whose previous DTaP vaccine doses have been with INFANRIX and/or PEDIARIX for the first 3 doses and INFANRIX for the fourth dose. (1)

**DOSAGE AND ADMINISTRATION**

A single intramuscular injection (0.5 mL). (2.2)

**DOSAGE FORMS AND STRENGTHS**

Single-dose vials and single-dose, prefilled syringes containing a 0.5-mL suspension for injection. (3)

**CONTRAINDICATIONS**

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, pertussis- or poliovirus-containing vaccine, or to any component of KINRIX, including neomycin and polymyxin B. (4.1)
- Encephalopathy within 7 days of administration of a previous pertussis-containing vaccine. (4.2)
- Progressive neurologic disorders. (4.3)

**WARNINGS AND PRECAUTIONS**

- If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior

vaccine containing tetanus toxoid, the decision to give KINRIX should be based on potential benefits and risks. (5.1)

- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.2)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including KINRIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.3)
- If temperature  $\geq 105^{\circ}\text{F}$ , collapse or shock-like state, or persistent, inconsolable crying lasting  $\geq 3$  hours have occurred within 48 hours after receipt of a pertussis-containing vaccine, or if seizures have occurred within 3 days after receipt of a pertussis-containing vaccine, the decision to give KINRIX should be based on potential benefits and risks. (5.4)
- For children at higher risk for seizures, an antipyretic may be administered at the time of vaccination with KINRIX. (5.5)

**ADVERSE REACTIONS**

- The most frequently reported solicited local reaction ( $>50\%$ ) was injection site pain. Other common solicited local reactions ( $\geq 25\%$ ) were redness, increase in arm circumference, and swelling. (6.1)
- Common solicited general adverse reactions ( $\geq 15\%$ ) were drowsiness, fever ( $\geq 99.5^{\circ}\text{F}$ ), and loss of appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

**DRUG INTERACTIONS**

Do not mix KINRIX with any other vaccine in the same syringe or vial. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/XXXX

**FULL PRESCRIBING INFORMATION: CONTENTS\*****1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

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- 2.2 Recommended Dose and Schedule

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\*Sections or subsections omitted from the full prescribing information are not listed.

## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

A single dose of KINRIX is indicated for active immunization against diphtheria, tetanus, pertussis, and poliomyelitis as the fifth dose in the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine series and the fourth dose in the inactivated poliovirus vaccine (IPV) series in children aged 4 through 6 years (prior to the 7<sup>th</sup> birthday) whose previous DTaP vaccine doses have been with INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) and/or PEDIARIX [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine] for the first 3 doses and INFANRIX for the fourth dose.

### **2 DOSAGE AND ADMINISTRATION**

#### **2.1 Preparation for Administration**

Shake vigorously to obtain a homogeneous, turbid, white suspension. Do not use if resuspension does not occur with vigorous shaking. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

For the prefilled syringes, attach a sterile needle and administer intramuscularly.

For the vials, use a sterile needle and sterile syringe to withdraw the 0.5-mL dose and administer intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. Use a separate sterile needle and syringe for each individual.

Do not administer this product intravenously, intradermally, or subcutaneously.

#### **2.2 Recommended Dose and Schedule**

KINRIX is to be administered as a 0.5-mL dose by intramuscular injection. The preferred site of administration is the deltoid muscle of the upper arm.

KINRIX may be used for the fifth dose in the DTaP immunization series and the fourth dose in the IPV immunization series in children aged 4 through 6 years (prior to the 7<sup>th</sup> birthday) whose previous DTaP vaccine doses have been with INFANRIX and/or PEDIARIX for the first 3 doses and INFANRIX for the fourth dose [*see Indications and Usage (1)*].

### **3 DOSAGE FORMS AND STRENGTHS**

KINRIX is a suspension for injection available in 0.5-mL single-dose vials and 0.5-mL single-dose prefilled TIP-LOK syringes.

## **4 CONTRAINDICATIONS**

### **4.1 Hypersensitivity**

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, pertussis- or poliovirus-containing vaccine, or to any component of KINRIX, including neomycin and polymyxin B, is a contraindication to administration of KINRIX [*see Description (11)*]. Because of the uncertainty as to which component of the vaccine might be responsible, no further vaccination with any of these components should be given. Alternatively, such individuals may be referred to an allergist for evaluation if immunization with any of these components is considered.

### **4.2 Encephalopathy**

Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of any pertussis-containing vaccine, including KINRIX.

### **4.3 Progressive Neurologic Disorder**

Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy, is a contraindication to administration of any pertussis-containing vaccine, including KINRIX. Pertussis vaccine should not be administered to individuals with such conditions until a treatment regimen has been established and the condition has stabilized.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Guillain-Barré Syndrome**

If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give any tetanus toxoid-containing vaccine, including KINRIX, should be based on careful consideration of the potential benefits and possible risks. When a decision is made to withhold tetanus toxoid, other available vaccines should be given, as indicated.

### **5.2 Latex**

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

### **5.3 Syncope**

Syncope (fainting) can occur in association with administration of injectable vaccines, including KINRIX. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

#### **5.4 Adverse Reactions following Prior Pertussis Vaccination**

If any of the following reactions occur in temporal relation to receipt of a pertussis-containing vaccine, the decision to give any pertussis-containing vaccine, including KINRIX, should be based on careful consideration of the potential benefits and possible risks:

- Temperature of  $\geq 40.5^{\circ}\text{C}$  ( $105^{\circ}\text{F}$ ) within 48 hours not due to another identifiable cause;
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours;
- Persistent, inconsolable crying lasting  $\geq 3$  hours, occurring within 48 hours;
- Seizures with or without fever occurring within 3 days.

When a decision is made to withhold pertussis vaccination, other available vaccines should be given, as indicated.

#### **5.5 Children at Risk for Seizures**

For children at higher risk for seizures than the general population, an appropriate antipyretic may be administered at the time of vaccination with a pertussis-containing vaccine, including KINRIX, and for the ensuing 24 hours to reduce the possibility of post-vaccination fever.

#### **5.6 Preventing and Managing Allergic Vaccine Reactions**

Prior to administration, the healthcare provider should review the patient's immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

### **6 ADVERSE REACTIONS**

#### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

A total of 4,013 children were vaccinated with a single dose of KINRIX in 4 clinical trials. Of these, 381 children received a non-U.S. formulation of KINRIX (containing  $\leq 2.5$  mg 2-phenoxyethanol per dose as preservative).

The primary study (Study 048), conducted in the United States, was a randomized, controlled clinical trial in which children aged 4 to 6 years were vaccinated with KINRIX ( $n = 3,156$ ) or control vaccines (INFANRIX and IPOL vaccine [IPV, Sanofi Pasteur SA];  $n = 1,053$ ) as a fifth DTap vaccine dose following 4 doses of INFANRIX and as a fourth IPV dose following 3 doses of IPOL. Subjects also received the second dose of U.S.-licensed measles, mumps, and rubella (MMR) vaccine (Merck & Co., Inc.) administered concomitantly, at separate sites.

Data on adverse events were collected by parents/guardians using standardized forms for 4

consecutive days following vaccination with KINRIX or control vaccines (i.e., day of vaccination and the next 3 days). The reported frequencies of solicited local reactions and general adverse reactions in Study 048 are presented in Table 1.

In 3 studies (Studies 046, 047, and 048), children were monitored for unsolicited adverse events, including serious adverse events that occurred in the 31-day period following vaccination, and in 2 studies (Studies 047 and 048), parents/guardians were actively queried about changes in the child's health status, including the occurrence of serious adverse events, through 6 months post-vaccination.



**Table 1. Percentage of Children Aged 4 to 6 Years Reporting Solicited Local or General Adverse Reactions within 4 Days of Vaccination<sup>a</sup> with KINRIX or Separate Concomitant Administration of INFANRIX and IPV when Coadministered with MMR Vaccine (Study 048) (Total Vaccinated Cohort)**

<b>Adverse Reaction</b>	<b>KINRIX</b>	<b>INFANRIX + IPV</b>
<b>Local<sup>b</sup></b>	<b>n = 3,121-3,128</b>	<b>n = 1,039-1,043</b>
Pain, any	57 <sup>c</sup>	53
Pain, Grade 2 or 3 <sup>d</sup>	14	12
Pain, Grade 3 <sup>d</sup>	2 <sup>c</sup>	1
Redness, any	37	37
Redness, ≥50 mm	18	20
Redness, ≥110 mm	3	4
Arm circumference increase, any	36	38
Arm circumference increase, >20 mm	7	7
Arm circumference increase, >30 mm	2	3
Swelling, any	26	27
Swelling, ≥50 mm	10	12
Swelling, ≥110 mm	1	2
<b>General</b>	<b>n = 3,037-3,120</b>	<b>n = 993-1,036</b>
Drowsiness, any	19	18
Drowsiness, Grade 3 <sup>e</sup>	1	1
Fever, ≥99.5°F	16	15
Fever, >100.4°F	7 <sup>c</sup>	4
Fever, >102.2°F	1	1
Fever, >104°F	0	0
Loss of appetite, any	16	16
Loss of appetite, Grade 3 <sup>f</sup>	1	1

IPV = Inactivated poliovirus vaccine (Sanofi Pasteur SA); MMR = Measles, mumps, and rubella vaccine (Merck & Co., Inc.).

Total Vaccinated Cohort = All vaccinated subjects for whom safety data were available.

n = Number of children with evaluable data for the reactions listed.

<sup>a</sup> Within 4 days of vaccination defined as day of vaccination and the next 3 days.

<sup>b</sup> Local reactions at the injection site for KINRIX or INFANRIX.

<sup>c</sup> Statistically higher than comparator group ( $P < 0.05$ ).

<sup>d</sup> Grade 2 defined as painful when the limb was moved; Grade 3 defined as preventing normal daily activities.

<sup>e</sup> Grade 3 defined as preventing normal daily activities.

<sup>f</sup> Grade 3 defined as not eating at all.

In Study 048, KINRIX was non-inferior to INFANRIX with regard to swelling that involved >50% of the injected upper arm length and that was associated with a >30 mm increase in mid-

upper arm circumference within 4 days following vaccination (upper limit of 2-sided 95% Confidence Interval for difference in percentage of KINRIX [0.6%, n = 20] minus INFANRIX [1.0%, n = 11]  $\leq 2\%$ ).

### Serious Adverse Events

Within the 31-day period following study vaccination in 3 studies (Studies 046, 047, and 048) in which all subjects received concomitant MMR vaccine (U.S.-licensed MMR vaccine [Merck & Co., Inc.] in Studies 047 and 048, non—U.S.-licensed MMR vaccine in Study 046), 3 subjects (0.1% [3/3,537]) who received KINRIX reported serious adverse events (dehydration and hypernatremia; cerebrovascular accident; dehydration and gastroenteritis) and 4 subjects (0.3% [4/1,434]) who received INFANRIX and inactivated poliovirus vaccine (Sanofi Pasteur SA) reported serious adverse events (cellulitis, constipation, foreign body trauma, fever without identified etiology).

## **6.2 Postmarketing Experience**

In addition to reports in clinical trials for KINRIX, the following adverse reactions have been identified during postapproval use of KINRIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccination.

### General Disorders and Administration Site Conditions

Injection site vesicles.

### Nervous System Disorders

Syncope.

### Skin and Subcutaneous Tissue Disorders

Pruritus.

Additional adverse reactions reported following postmarketing use of INFANRIX, for which a causal relationship to vaccination is plausible, are: Allergic reactions, including anaphylactoid reactions, anaphylaxis, angioedema, and urticaria; apnea; collapse or shock-like state (hypotonic-hyporesponsive episode); convulsions (with or without fever); lymphadenopathy; and thrombocytopenia.

## **7 DRUG INTERACTIONS**

### **7.1 Concomitant Vaccine Administration**

In U.S. clinical trials, KINRIX was administered concomitantly with the second dose of MMR vaccine (Merck & Co., Inc.); in one of these trials (Study 055), KINRIX was also administered concomitantly with varicella vaccine (Merck & Co., Inc.) [*see Clinical Studies (14.2)*].

When KINRIX is administered concomitantly with other injectable vaccines, they should be

given with separate syringes. KINRIX should not be mixed with any other vaccine in the same syringe or vial.

## **7.2 Immunosuppressive Therapies**

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to KINRIX.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.4 Pediatric Use**

Safety and effectiveness of KINRIX in children younger than 4 years and children aged 7 to 16 years have not been evaluated. KINRIX is not approved for use in persons in these age groups.

## **11 DESCRIPTION**

KINRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine) is a noninfectious, sterile vaccine for intramuscular administration. Each 0.5-mL dose is formulated to contain 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, 25 mcg of inactivated pertussis toxin (PT), 25 mcg of filamentous hemagglutinin (FHA), 8 mcg of pertactin (69 kiloDalton outer membrane protein), 40 D-antigen Units (DU) of Type 1 poliovirus (Mahoney), 8 DU of Type 2 poliovirus (MEF-1), and 32 DU of Type 3 poliovirus (Saukett). The diphtheria, tetanus, and pertussis components of KINRIX are the same as those in INFANRIX and PEDIARIX and the poliovirus component is the same as that in PEDIARIX.

The diphtheria toxin is produced by growing *Corynebacterium diphtheriae* (*C. diphtheriae*) in Fenton medium containing a bovine extract. Tetanus toxin is produced by growing *Clostridium tetani* (*C. tetani*) in a modified Latham medium derived from bovine casein. The bovine materials used in these extracts are sourced from countries which the United States Department of Agriculture (USDA) has determined neither have nor are at risk of bovine spongiform encephalopathy (BSE). Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and purified by precipitation, dialysis, and sterile filtration.

The acellular pertussis antigens (PT, FHA, and pertactin) are isolated from *Bordetella pertussis* (*B. pertussis*) culture grown in modified Stainer-Scholte liquid medium. PT and FHA are isolated from the fermentation broth; pertactin is extracted from the cells by heat treatment and flocculation. The antigens are purified in successive chromatographic and precipitation steps. PT is detoxified using glutaraldehyde and formaldehyde. FHA and pertactin are treated with formaldehyde.

Diphtheria and tetanus toxoids and pertussis antigens (inactivated PT, FHA, and pertactin) are individually adsorbed onto aluminum hydroxide.

The inactivated poliovirus component of KINRIX is an enhanced potency component. Each of the 3 strains of poliovirus is individually grown in VERO cells, a continuous line of monkey kidney cells, cultivated on microcarriers. Calf serum and lactalbumin hydrolysate are used during VERO cell culture and/or virus culture. Calf serum is sourced from countries the USDA has determined neither have nor are at risk of BSE. After clarification, each viral suspension is purified by ultrafiltration, diafiltration, and successive chromatographic steps, and inactivated with formaldehyde. The 3 purified viral strains are then pooled to form a trivalent concentrate.

Diphtheria and tetanus toxoid potency is determined by measuring the amount of neutralizing antitoxin in previously immunized guinea pigs. The potency of the acellular pertussis components (inactivated PT, FHA, and pertactin) is determined by enzyme-linked immunosorbent assay (ELISA) on sera from previously immunized mice. The potency of the inactivated poliovirus component is determined by using the D-antigen ELISA and by a poliovirus-neutralizing cell culture assay on sera from previously immunized rats.

Each 0.5-mL dose contains aluminum hydroxide as adjuvant (not more than 0.6 mg aluminum by assay) and 4.5 mg of sodium chloride. Each dose also contains  $\leq 100$  mcg of residual formaldehyde and  $\leq 100$  mcg of polysorbate 80 (Tween 80). Neomycin sulfate and polymyxin B are used in the poliovirus vaccine manufacturing process and may be present in the final vaccine at  $\leq 0.05$  ng neomycin and  $\leq 0.01$  ng polymyxin B per dose.

The tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with natural rubber latex. The vial stoppers are not made with natural rubber latex.

KINRIX does not contain a preservative.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

#### Diphtheria

Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection; a level of 0.1 IU/mL is regarded as protective.<sup>1</sup>

#### Tetanus

Tetanus is an acute toxin-mediated disease caused by a potent exotoxin released by *C. tetani*. Protection against disease is due to the development of neutralizing antibodies to the tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assays, is considered the minimum protective level.<sup>2,3</sup> A level of  $\geq 0.1$  IU/mL is considered protective.<sup>4</sup>

#### Pertussis

Pertussis (whooping cough) is a disease of the respiratory tract caused by *B. pertussis*. The role

of the different components produced by *B. pertussis* in either the pathogenesis of, or the immunity to, pertussis is not well understood. There is no well-established serological correlate of protection for pertussis. The efficacy of the pertussis component of KINRIX was determined in clinical trials of INFANRIX administered as a 3-dose series in infants (see INFANRIX prescribing information).

### Poliomyelitis

Poliovirus is an enterovirus that belongs to the picornavirus family. Three serotypes of poliovirus have been identified (Types 1, 2, and 3). Neutralizing antibodies against the 3 poliovirus serotypes are recognized as conferring protection against poliomyelitis disease.<sup>5</sup>

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

KINRIX has not been evaluated for carcinogenic or mutagenic potential or for impairment of fertility.

## **14 CLINICAL STUDIES**

### **14.1 Immunological Evaluation**

In a U.S. multicenter study (Study 048), 4,209 children were randomized in a 3:1 ratio to receive either KINRIX or INFANRIX and IPV (Sanofi Pasteur SA) administered concomitantly at separate sites. Subjects also received MMR vaccine (Merck & Co., Inc.) administered concomitantly at a separate site. Subjects were children aged 4 through 6 years who previously received 4 doses of INFANRIX, 3 doses of IPV, and 1 dose of MMR vaccine. Among subjects in both vaccine groups combined, 49.6% were female; 45.6% of subjects were white, 18.8% Hispanic, 13.6% Asian, 7.0% black, and 15.0% were of other racial/ethnic groups.

Levels of antibodies to the diphtheria, tetanus, pertussis (PT, FHA, and pertactin), and poliovirus antigens were measured in sera obtained immediately prior to vaccination and 1 month (range: 31 to 48 days) after vaccination (Table 2). The co-primary immunogenicity endpoints were anti-diphtheria toxoid, anti-tetanus toxoid, anti-PT, anti-FHA, and anti-pertactin booster responses, and anti-poliovirus Type 1, Type 2, and Type 3 geometric mean antibody titers (GMTs) 1 month after vaccination. KINRIX was shown to be non-inferior to INFANRIX and IPV administered separately, in terms of booster responses to DTaP antigens and post-vaccination GMTs for anti-poliovirus antibodies (Table 2).

**Table 2. Pre-Vaccination Antibody Levels and Post-Vaccination<sup>a</sup> Antibody Responses following KINRIX Compared with Separate Concomitant Administration of INFANRIX and IPV in Children Aged 4 to 6 Years when Coadministered with MMR Vaccine (Study 048) (ATP Cohort for Immunogenicity)**

	<b>KINRIX n = 787-851</b>	<b>INFANRIX + IPV n = 237-262</b>
<b>Anti-diphtheria Toxoid</b>		
Pre-vaccination % $\geq 0.1$ IU/mL (95% CI) <sup>b</sup>	87.7 (85.3, 89.9)	85.5 (80.6, 89.5)
Post-vaccination % $\geq 0.1$ IU/mL (95% CI) <sup>b</sup>	100 (99.6, 100)	100 (98.6, 100)
% Booster Response (95% CI) <sup>c</sup>	99.5 (98.8, 99.9) <sup>d</sup>	100 (98.6, 100)
<b>Anti-tetanus Toxoid</b>		
Pre-vaccination % $\geq 0.1$ IU/mL (95% CI) <sup>b</sup>	87.8 (85.4, 90.0)	88.2 (83.6, 91.8)
Post-vaccination % $\geq 0.1$ IU/mL (95% CI) <sup>b</sup>	100 (99.6, 100)	100 (98.6, 100)
% Booster Response (95% CI) <sup>c</sup>	96.7 (95.2, 97.8) <sup>d</sup>	93.9 (90.2, 96.5)
<b>Anti-PT</b>		
% Booster Response (95% CI) <sup>c</sup>	92.2 (90.2, 94.0) <sup>d</sup>	92.6 (88.7, 95.5)
<b>Anti-FHA</b>		
% Booster Response (95% CI) <sup>c</sup>	95.4 (93.7, 96.7) <sup>d</sup>	96.2 (93.1, 98.1)
<b>Anti-pertactin</b>		
% Booster Response (95% CI) <sup>c</sup>	97.8 (96.5, 98.6) <sup>d</sup>	96.9 (94.1, 98.7)
<b>Anti-poliovirus 1</b>		
Pre-vaccination % $\geq 1:8$ (95% CI) <sup>b</sup>	88.3 (85.9, 90.4)	85.1 (80.1, 89.2)
Post-vaccination % $\geq 1:8$ (95% CI) <sup>b</sup>	99.9 (99.3, 100)	100 (98.5, 100)
Post-vaccination GMT (95% CI)	2,127 (1,976, 2,290) <sup>f</sup>	1,685 (1,475, 1,925)
<b>Anti-poliovirus 2</b>		
Pre-vaccination % $\geq 1:8$ (95% CI) <sup>b</sup>	91.8 (89.7, 93.6)	87.0 (82.3, 90.8)
Post-vaccination % $\geq 1:8$ (95% CI) <sup>b</sup>	100 (99.6, 100)	100 (98.5, 100)
Post-vaccination GMT (95% CI)	2,265 (2,114, 2,427) <sup>f</sup>	1,818 (1,606, 2,057)
<b>Anti-poliovirus 3</b>		
Pre-vaccination % $\geq 1:8$ (95% CI) <sup>b</sup>	84.7 (82.0, 87.0)	85.0 (80.1, 89.1)
Post-vaccination % $\geq 1:8$ (95% CI) <sup>b</sup>	100 (99.5, 100)	100 (98.5, 100)
Post-vaccination GMT (95% CI)	3,588 (3,345, 3,849) <sup>f</sup>	3,365 (2,961, 3,824)

ATP = According-to-protocol; CI = Confidence Interval; GMT = Geometric mean antibody titer; IPV = Inactivated poliovirus vaccine (Sanofi Pasteur SA); MMR = Measles, mumps, and rubella vaccine (Merck & Co., Inc.).

n = Number of subjects with available results.

<sup>a</sup> One-month blood sampling, range 31 to 48 days.

<sup>b</sup> Seroprotection defined as anti-diphtheria toxoid and anti-tetanus toxoid antibody concentrations  $\geq 0.1$  IU/mL by ELISA and as anti-poliovirus Type 1, Type 2, and Type 3 antibody titer  $\geq 1:8$  by micro-neutralization assay for poliovirus.

<sup>c</sup> Booster response: In subjects with pre-vaccination  $< 0.1$  IU/mL, post-vaccination concentration  $\geq 0.4$  IU/mL. In subjects with pre-vaccination concentration  $\geq 0.1$  IU/mL, an increase of at least 4 times the pre-vaccination concentration.

<sup>d</sup> KINRIX was non-inferior to INFANRIX + IPV based on booster response rates (upper limit of 2-sided 95% CI on the difference of INFANRIX + IPV minus KINRIX  $\leq 10\%$ ).

<sup>e</sup> Booster response: In subjects with pre-vaccination  $< 5$  EL.U./mL, post-vaccination concentration  $\geq 20$  EL.U./mL. In subjects with pre-vaccination  $\geq 5$  EL.U./mL and  $< 20$  EL.U./mL, an increase of at least 4 times the pre-vaccination concentration. In subjects with pre-vaccination  $\geq 20$  EL.U./mL, an increase of at least 2 times the pre-vaccination concentration.

<sup>f</sup> KINRIX was non-inferior to INFANRIX + IPV based on post-vaccination anti-poliovirus antibody GMTs adjusted for baseline titer (upper limit of 2-sided 95% CI for the GMT ratio [INFANRIX + IPV:KINRIX]  $\leq 1.5$ ).

## 14.2 Concomitant Vaccine Administration

In a U.S. study (Study 055) that enrolled children aged 4 to 6 years, KINRIX was administered concomitantly at separate sites with MMR vaccine (Merck & Co., Inc.) ( $n = 237$ ) or with MMR vaccine and varicella vaccine (Merck & Co., Inc.) ( $n = 239$ ). Immune responses to the antigens contained in KINRIX were measured approximately 1 month (28 to 48 days) after vaccination. Booster responses to diphtheria, tetanus, and pertussis antigens and GMTs for poliovirus (Type 1, 2, and 3) after the receipt of KINRIX administered concomitantly with MMR vaccine and varicella vaccine were non-inferior to immune responses following concomitant administration of KINRIX administered with MMR vaccine.

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## 16 HOW SUPPLIED/STORAGE AND HANDLING

KINRIX is available in 0.5-mL single-dose vials and 0.5-mL single-dose, disposable, prefilled TIP-LOK syringes (packaged without needles):

NDC 58160-812-01 Vial in Package of 10: NDC 58160-812-11

NDC 58160-812-43 Syringe in Package of 10: NDC 58160-812-52

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen.

## 17 PATIENT COUNSELING INFORMATION

Provide the following information to the parent or guardian:

- Inform of the potential benefits and risks of immunization with KINRIX.
- Inform about the potential for adverse reactions that have been temporally associated with administration of KINRIX or other vaccines containing similar components.
- Give the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).

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KNX:XXPI

# **EXHIBIT 263**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Quadracel safely and effectively. See full prescribing information for Quadracel.

**Quadracel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine)  
Suspension for Intramuscular Injection  
Initial U.S. Approval: 2015**

### INDICATIONS AND USAGE

Quadracel is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis and poliomyelitis. A single dose of Quadracel is approved for use in children 4 through 6 years of age as a fifth dose in the diphtheria, tetanus, pertussis vaccination (DTaP) series, and as a fourth or fifth dose in the inactivated poliovirus vaccination (IPV) series, in children who have received 4 doses of Pentacel and/or DAPTACEL vaccine. (1)

### DOSAGE AND ADMINISTRATION

A single intramuscular injection of 0.5 mL. (2)

### DOSAGE FORMS AND STRENGTHS

Suspension for injection, supplied in single-dose (0.5 mL) vials. (3)

### CONTRAINDICATIONS

- Severe allergic reaction (e.g., anaphylaxis) to any ingredient of Quadracel, or following any diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine or inactivated poliovirus vaccine. (4.1) (11)
- Encephalopathy within 7 days of a previous pertussis-containing vaccine with no other identifiable cause. (4.2)

- Progressive neurologic disorder until a treatment regimen has been established and the condition has stabilized. (4.3)

### WARNINGS AND PRECAUTIONS

- Carefully consider benefits and risks before administering Quadracel to persons with a history of:
  - fever  $\geq 40.5^{\circ}\text{C}$  ( $\geq 105^{\circ}\text{F}$ ), hypotonic-hyporesponsive episode (HHE) or persistent, inconsolable crying lasting  $\geq 3$  hours within 48 hours after a previous pertussis-containing vaccine. (5.2)
  - seizures within 3 days after a previous pertussis-containing vaccine. (5.2)
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give any tetanus toxoid-containing vaccine, including Quadracel, should be based on careful consideration of the potential benefits and possible risks. (5.3)

### ADVERSE REACTIONS

In a clinical study, the most common solicited injection site reactions were pain ( $>75\%$ ), increase in arm circumference ( $>65\%$ ), erythema ( $>55\%$ ), and swelling ( $>40\%$ ). Common solicited systemic reactions were myalgia ( $>50\%$ ), malaise ( $>35\%$ ), and headache ( $>15\%$ ). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or <http://vaers.hhs.gov>

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2019

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

Quadracel® is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis and poliomyelitis. A single dose of Quadracel is approved for use in children 4 through 6 years of age as a fifth dose in the diphtheria, tetanus, pertussis vaccination (DTaP) series, and as a fourth or fifth dose in the inactivated poliovirus vaccination (IPV) series, in children who have received 4 doses of Pentacel® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus and *Haemophilus b* conjugate (Tetanus Toxoid Conjugate) Vaccine] and/or DAPTACEL® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed).

### **2 DOSAGE AND ADMINISTRATION**

#### **For intramuscular use only.**

Just before use, shake the vial well, until a uniform, white, cloudy suspension results. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exist, the product should not be administered.

Withdraw and administer a 0.5 mL dose of Quadracel vaccine intramuscularly into the deltoid muscle of the upper arm. Discard unused portion.

Quadracel should not be combined through reconstitution or mixed with any other vaccine.

### **3 DOSAGE FORMS AND STRENGTHS**

Quadracel is a suspension for injection in 0.5 mL single-dose vials.

### **4 CONTRAINDICATIONS**

#### **4.1 Hypersensitivity**

Severe allergic reaction (e.g., anaphylaxis) to any ingredient of Quadracel [see *Description (11)*] or following any diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, or inactivated poliovirus vaccine, is a contraindication to administration of Quadracel.

#### **4.2 Encephalopathy**

Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of any pertussis-containing vaccine, including Quadracel.

#### **4.3 Progressive Neurologic Disorder**

Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy is a contraindication to administration of any pertussis-containing vaccine including Quadracel. Pertussis vaccine should not be administered to individuals with such conditions until a treatment regimen has been established and the condition has stabilized.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Management of Acute Allergic Reactions**

Epinephrine hydrochloride solution (1:1,000) and other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

### **5.2 Adverse Reactions Following Prior Pertussis Vaccination**

If any of the following events have occurred within the specified period after administration of a pertussis vaccine, the decision to administer Quadracel should be based on careful consideration of benefits and risks.

- Temperature of  $\geq 40.5^{\circ}\text{C}$  ( $\geq 105^{\circ}\text{F}$ ) within 48 hours, not attributable to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode [HHE]) within 48 hours.
- Persistent, inconsolable crying lasting  $\geq 3$  hours within 48 hours.
- Seizures with or without fever within 3 days.

### **5.3 Guillain-Barré Syndrome**

If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give any vaccine containing tetanus toxoid, including Quadracel, should be based on careful consideration of the potential benefits and possible risks.

### **5.4 Limitations of Vaccine Effectiveness**

Vaccination with Quadracel may not protect all individuals.

### **5.5 Altered Immunocompetence**

If Quadracel is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained [see *Drug Interactions* (7.2)].

## **6 ADVERSE REACTIONS**

In a clinical study, the most common solicited injection site reactions were pain ( $>75\%$ ), increase in arm circumference ( $>65\%$ ), erythema ( $>55\%$ ), and swelling ( $>40\%$ ). Common solicited systemic reactions were myalgia ( $>50\%$ ), malaise ( $>35\%$ ), and headache ( $>15\%$ ).

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events. The poliovirus component (poliovirus types 1, 2, and 3) of this formulation of Quadracel is grown in Vero cells [see *Description* (11)]. The clinical study data in this section were accrued with a Quadracel formulation in which poliovirus component was grown in MRC-5 cells.

In a randomized, controlled, multicenter study conducted in the US and Puerto Rico (Study M5I02; ClinicalTrials.gov Identifier: NCT01346293), 3,372 children, 4 to 6 years of age, who had received 4 doses of DAPTACEL and/or Pentacel vaccine(s) received Quadracel, or DAPTACEL + IPOL (Poliovirus Vaccine Inactivated) vaccines administered concomitantly but at separate sites. Subjects also received Measles, Mumps, and Rubella Virus Vaccine Live (MMR) (Merck & Co., Inc.) and Varicella Virus Vaccine Live (Varicella vaccine) (Merck & Co., Inc.) administered concomitantly at separate sites. Safety was evaluated in 2,733 subjects who received Quadracel and 621 subjects who received DAPTACEL + IPOL vaccines.

Among these subjects, 51.5% were male, 48.5% were female, 75.7% were Caucasian, 8.6% were Black, 7.9% were Hispanic, 0.9% were Asian, and 7.8% were of other racial/ethnic groups. The mean age for both groups was 4.4 years and the ratio of male to female subjects and ethnicity were balanced between both groups.

Solicited injection site reactions and systemic reactions were collected daily for 7 days following vaccination, via diary cards. Participants were monitored for unsolicited adverse events for 28 days and serious adverse events (SAEs) for 6 months after vaccination.

#### **Solicited Adverse Reactions**

The incidence and severity of solicited injection site and systemic adverse reactions that occurred within 7 days after vaccination in each study group are shown in Table 1.

**Table 1: Percentage of Children 4 through 6 years of Age with Solicited Adverse Reactions by Intensity Within 7 Days of Vaccination with Quadracel or Concomitant but Separate DAPTACEL and IPOL vaccines Co-Administered with MMR and Varicella Vaccines\***

		<b>Quadracel (N†= 2,500-2,689)</b>	<b>DAPTACEL + IPOL (N†= 598-603)</b>
<b>Injection Site Reactions</b>		Quadracel site	DAPTACEL or IPOL site
<b>Pain‡</b>	Any	77.4	76.5
	Grade 1	56.4	54.9
	Grade 2	19.0	18.6
	Grade 3	2.0	3.0
<b>Change in limb circumference§</b>	Any	68.1	65.1
	Grade 1	59.8	58.6
	Grade 2	8.2	6.5
	Grade 3	0.2	0.0
<b>Erythema</b>	Any	59.1	53.4
	>0 to <25 mm	31.6	31.8
	≥25 to <50 mm	9.5	9.6
	≥50 mm	18.0	11.9
<b>Swelling</b>	Any	40.2	36.4
	>0 to <25 mm	23.5	23.1
	≥25 to <50 mm	8.1	6.1
	≥50 mm	8.6	7.1
<b>Extensive limb swelling¶</b>	Any	1.5	1.3
<b>Systemic Reactions</b>			
<b>Myalgia#</b>	Any	53.8	52.6
	Grade 1	36.0	33.5
	Grade 2	15.8	16.3
	Grade 3	1.9	2.8
<b>Malaise#</b>	Any	35.0	33.2
	Grade 1	21.7	18.7
	Grade 2	10.6	11.1
	Grade 3	2.6	3.3
<b>Headache#</b>	Any	15.6	16.6
	Grade 1	11.9	11.9
	Grade 2	3.1	4.0
	Grade 3	0.6	0.7
<b>Fever</b>	Any	6.0	6.9
	≥38.0°C to ≤38.4°C	2.6	3.0
	≥38.5°C to ≤38.9°C	2.1	1.8
	≥39.0°C	1.3	2.0

\* ClinicalTrials.gov Identifier: NCT01346293.



† N = The number of subjects with available data.

‡ Grade 1: Easily tolerated, Grade 2: Sufficiently discomforting to interfere with normal behavior or activities, Grade 3: Incapacitating, unable to perform usual activities.

§ Grade 1: >0 to <25 mm increase over pre-vaccination measurement, Grade 2: ≥25 to ≤50 mm increase over pre-vaccination measurement, Grade 3: >50 mm increase over pre-vaccination measurement.

¶ Swelling of the injected limb including the adjacent joint (i.e., elbow and/or shoulder) as compared to baseline.

# Grade 1: No interference with activity, Grade 2: Some interference with activity, Grade 3: Significant; prevents daily activity.

### Serious Adverse Events

In Study M5I02, within 28 days following vaccination with Quadracel, or DAPTACEL + IPOL vaccines, and concomitant MMR and varicella vaccines, 0.1% of subjects (3/2,733) in the Quadracel group experienced a serious adverse event. During the same time period, 0.2% subjects (1/621) in the DAPTACEL + IPOL group experienced a SAE. Within the 6-month follow-up period after vaccination, SAEs were reported in 0.8% of subjects (21/2,733) who received Quadracel and 0.5% of subjects (3/621) who received DAPTACEL + IPOL vaccines, none of which were assessed as related to vaccination.

## 6.2 Postmarketing Experience

The following adverse events have been spontaneously reported, during the post-marketing use of Quadracel outside the US, in infants and children from 2 months through 6 years of age. Because these events are reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency reliably or establish a causal relationship to vaccine exposure. This list includes adverse events based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to Quadracel.

- **Immune system disorders**  
Anaphylactic reaction, hypersensitivity and allergic reactions (such as rash, urticaria, dyspnea)
- **Psychiatric disorders**  
Screaming
- **Nervous system disorders**  
Somnolence, convulsion, febrile convulsion, HHE, hypotonia
- **Cardiac disorders**  
Cyanosis
- **Vascular disorders**  
Pallor
- **General disorders and administration site conditions**  
Listlessness  
Injection site reactions (including inflammation, mass, sterile abscess, and edema)  
Large injection site reactions (>50 mm), including limb swelling which may extend from the injection site beyond one or both joints
- **Infections and Infestations**  
Injection site cellulitis, injection site abscess

## **7 DRUG INTERACTIONS**

### **7.1 Concomitant Administration with Other Vaccines**

In the US clinical trial, Study M5I02, Quadracel was administered concomitantly with one or more of the following US-licensed vaccines: MMR vaccine and varicella vaccine [see *Adverse Reactions* (6.1)].

When Quadracel is given at the same time as another injectable vaccine(s), the vaccines should be administered with different syringes and at different injection sites.

### **7.2 Immunosuppressive Treatments**

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to Quadracel [see *Warnings and Precautions* (5.5)].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.4 Pediatric Use**

The safety and effectiveness of Quadracel has not been established in children less than 4 years of age or children 7 through 16 years of age and is not approved for use in these age groups.

## **11 DESCRIPTION**

Quadracel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine) is a sterile suspension for intramuscular injection.

Each 0.5 mL dose is formulated to contain 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, acellular pertussis antigens [20 mcg detoxified pertussis toxin (PT), 20 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)], and inactivated polioviruses [29 D-antigen units (DU) Type 1 (Mahoney), 7 DU Type 2 (MEF-1), 26 DU Type 3 (Saukett)].

*Corynebacterium diphtheriae* is grown in modified Mueller's growth medium. (1) After purification by ammonium sulfate fractionation, the diphtheria toxin is detoxified with formaldehyde and diafiltered.

*Clostridium tetani* is grown in modified Mueller-Miller casamino acid medium without beef heart infusion. (2) Tetanus toxin is detoxified with formaldehyde and purified by ammonium sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

The acellular pertussis vaccine antigens are produced from *Bordetella pertussis* cultures grown in Stainer-Scholte medium (3) modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium. FIM are extracted and copurified from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde. FHA is treated with formaldehyde and the residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed separately onto aluminum phosphate.

The Type 1, Type 2, and Type 3 polioviruses are individually grown in Vero cells (a continuous line of monkey kidney cells). Prior to viral propagation, the cells are grown in Iscove's medium, supplemented with calf serum. For viral propagation, the culture medium is replaced by M199 medium without calf serum. The viral harvests are concentrated and purified, then inactivated with formaldehyde to produce monovalent suspensions of each serotype. Specified quantities of monovalent suspensions of each serotype are mixed to produce the trivalent poliovirus concentrate. The adsorbed diphtheria, tetanus and acellular pertussis antigens are combined with aluminum phosphate, 2-phenoxyethanol (not as a preservative) and water for injection, into an intermediate concentrate. The trivalent poliovirus concentrate is added and the vaccine is diluted to its final concentration.

Each 0.5 mL dose contains 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, <8.1 mcg polysorbate 80, 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative), 2 mcg to 7 mcg residual formaldehyde, <50 ng residual glutaraldehyde, ≤10 ng residual bovine serum albumin, <0.0001 pg streptomycin sulphate, <0.01 pg of neomycin and <0.000001 pg polymyxin B sulphate.

Quadracel does not contain a preservative.

Both diphtheria and tetanus toxoids induce at least 2 neutralizing units per mL in the guinea pig potency test. The potency of the acellular pertussis antigens is evaluated by the antibody response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by enzyme-linked immunosorbent assay (ELISA). The potency of the inactivated poliovirus antigens is determined by measuring antibody-mediated neutralization of poliovirus in sera from immunized rats.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

#### **Diphtheria**

Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (4) Levels of 1.0 IU/mL have been associated with long-term protection. (5)

#### **Tetanus**

Tetanus is an acute disease caused by an extremely potent neurotoxin produced by *C. tetani*. Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay, is considered the minimum protective level. (4) (6). A tetanus antitoxoid level ≥0.1 IU/mL as measured by the ELISA used in clinical studies of Quadracel is considered protective.

#### **Pertussis**

Pertussis (whooping cough) is a respiratory disease caused by *B. pertussis*. This Gram-negative coccobacillus produces a variety of biologically active components, though their role in either the pathogenesis of, or immunity to, pertussis has not been clearly defined.

There is no well-established serological correlate of protection for pertussis. Because DAPTACEL contains the same pertussis antigens manufactured by the same process as those in Quadracel, the effectiveness of Quadracel against pertussis was based on a comparison of pertussis immune responses following Quadracel to those following DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) [see *Clinical Studies (14)*]. The efficacy of the pertussis component of DAPTACEL was determined in clinical trials of DAPTACEL administered to infants (see DAPTACEL prescribing information). Quadracel contains twice as much detoxified PT and four times as much FHA as DAPTACEL.

### Poliomyelitis

Polioviruses, of which there are three serotypes (Types 1, 2, and 3), are enteroviruses. The presence of poliovirus type-specific neutralizing antibodies has been correlated with protection against poliomyelitis. (7)

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Quadracel has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

## **14 CLINICAL STUDIES**

The poliovirus component (poliovirus types 1, 2 and 3) of this formulation of Quadracel is grown in Vero cells [see *Description (11)*]. The clinical study data in this section were accrued with a Quadracel formulation in which the poliovirus component was grown in MRC-5 cells. The poliovirus component of the two formulations of Quadracel are analytically comparable.

### **14.1 Immunogenicity**

In Study M5I02, children 4 through 6 years of age received Quadracel or DAPTACEL + IPOL as the fifth dose in the diphtheria, tetanus, and pertussis vaccination series and the fourth or fifth dose in the inactivated poliovirus vaccination series. Subjects also received their second dose of MMR and Varicella vaccines, concomitantly. The immunogenicity subset comprised 263 subjects in the Quadracel group and 253 subjects in the DAPTACEL + IPOL vaccines group [see *Clinical Trials Experience (6.1)*].

Antibody levels to diphtheria, tetanus, pertussis (PT, FHA, PRN and FIM) and poliovirus antigens were measured in sera obtained immediately prior to vaccination and 28 days after vaccination. The co-primary endpoints were booster response rates and antibody geometric mean concentrations/titers (GMCs/GMTs) to diphtheria, tetanus, pertussis and poliovirus antigens elicited after vaccination. Booster response rates and antibody GMCs/GMTs following Quadracel vaccination were compared to those after DAPTACEL + IPOL vaccination.

Quadracel was non-inferior to DAPTACEL + IPOL vaccines administered concomitantly at separate sites, as demonstrated by comparison of the post-vaccination antibody booster response rates and GMCs/GMTs to diphtheria and tetanus (Table 2), to all pertussis antigens (Table 3) and to poliovirus 1, 2 and 3 (Table 4).

**Table 2: Booster Response Rates, Pre- and Post-Vaccination Seroprotection Rates and Post-Vaccination Antibody Levels to Diphtheria and Tetanus Antigens Following Quadracel or Concomitant but Separate DAPTACEL and IPOL Vaccines Co-Administered with MMR and Varicella Vaccines\***

	<b>Quadracel (N<sup>†</sup>=253-262)</b>	<b>DAPTACEL + IPOL (N<sup>†</sup>=248-253)</b>
<b>Anti-Diphtheria</b>		
% Booster Response <sup>‡</sup>	97.3 <sup>§</sup>	99.2
Pre-vaccination % $\geq 0.1$ IU/mL <sup>¶</sup>	90.7	83.1
Post-vaccination % $\geq 0.1$ IU/mL <sup>¶</sup>	100.0	99.6
Post-vaccination % $\geq 1.0$ IU/mL <sup>¶</sup>	99.6	99.6
Post-vaccination GMC (IU/mL)	18.6 <sup>#</sup>	15.5
<b>Anti-Tetanus</b>		
% Booster Response <sup>‡</sup>	84.2 <sup>§</sup>	84.3
Pre-vaccination % $\geq 0.1$ IU/mL <sup>¶</sup>	91.7	89.1
Post-vaccination % $\geq 0.1$ IU/mL <sup>¶</sup>	100.0	99.2
Post-vaccination % $\geq 1.0$ IU/mL <sup>¶</sup>	98.9	96.8
Post-vaccination GMC (IU/mL)	6.4 <sup>#</sup>	5.5

\* ClinicalTrials.gov Identifier: NCT01346293.

<sup>†</sup> N = The number of subjects with available data.

<sup>‡</sup> Booster response: In subjects with pre-vaccination antibody concentrations  $< 0.1$  IU/mL, a post-vaccination level  $\geq 0.4$  IU/mL; in subjects with pre-vaccination antibody concentrations  $\geq 0.1$  IU/mL but  $< 2.0$  IU/mL, a 4-fold rise in post-vaccination level; in subjects with pre-vaccination antibody level  $\geq 2.0$  IU/mL, a 2-fold rise in post-vaccination level.

<sup>§</sup> Quadracel was non-inferior to DAPTACEL + IPOL based on the post-vaccination booster response rates for diphtheria and tetanus (lower limits of the 2-sided 95% CIs of the difference [Quadracel minus DAPTACEL + IPOL] were  $> -10\%$ ).

<sup>¶</sup> Seroprotection: anti-diphtheria and anti-tetanus antibody concentrations  $\geq 0.1$  IU/mL and  $\geq 1.0$  IU/mL.

<sup>#</sup> Quadracel was non-inferior to DAPTACEL + IPOL based on the post-vaccination GMCs for diphtheria and tetanus (lower limits of the 2-sided 95% CIs of the ratio [Quadracel / DAPTACEL + IPOL] were  $> 2/3$ ).

**Table 3: Booster Response Rates and Post-vaccination Antibody Levels to Pertussis Antigens Following Quadracel or Concomitant but Separate DAPTACEL and IPOL Vaccines Co-Administered with MMR and Varicella Vaccines\***

	<b>Quadracel (N<sup>†</sup>=250-255)</b>	<b>DAPTACEL + IPOL (N<sup>†</sup>=247-249)</b>
<b>Anti-PT</b>		
% Booster Response <sup>‡</sup>	95.2 <sup>§</sup>	89.9
Post-vaccination GMC (EU/mL)	120.7 <sup>¶</sup>	61.3
<b>Anti-FHA</b>		
% Booster Response <sup>‡</sup>	94.9 <sup>§</sup>	87.5
Post-vaccination GMC (EU/mL)	123.5 <sup>¶</sup>	79.0
<b>Anti-PRN</b>		
% Booster Response <sup>‡</sup>	96.9 <sup>§</sup>	93.1
Post-vaccination GMC (EU/mL)	282.6 <sup>¶</sup>	187.5
<b>Anti-FIM</b>		
% Booster Response <sup>‡</sup>	97.2 <sup>§</sup>	92.4
Post-vaccination GMC (EU/mL)	505.8 <sup>¶</sup>	378.9

\* ClinicalTrials.gov Identifier: NCT01346293.

<sup>†</sup> N = The number of subjects with available data.

<sup>‡</sup> Booster response: In subjects with pre-vaccination antibody concentrations <LLOQ, a post-vaccination level  $\geq 4 \times \text{LLOQ}$ ; in subjects with pre-vaccination antibody concentrations  $\geq \text{LLOQ}$  but  $< 4 \times \text{LLOQ}$ , a 4-fold rise in post-vaccination level; in subjects with pre-vaccination antibody level  $\geq 4 \times \text{LLOQ}$ , a 2-fold rise in post-vaccination level.

<sup>§</sup> Quadracel was non-inferior to DAPTACEL + IPOL based on the post-vaccination booster response rates for all pertussis antigens (lower limits of the 2-sided 95% CIs of the difference [Quadracel minus DAPTACEL + IPOL] were  $> -10\%$ ).

<sup>¶</sup> Quadracel was non-inferior to DAPTACEL + IPOL based on the post-vaccination GMCs for all pertussis antigens (lower limits of the 2-sided 95% CIs of the ratio [DTaP-IPV / DAPTACEL + IPOL] were  $> 2/3$ ).

**Table 4: Booster Response Rates, Pre- and Post-Vaccination Seroprotection Rates and Post-vaccination Antibody Levels to Poliovirus Antigens Following Quadracel or Concomitant but Separate DAPTACEL and IPOL Vaccines Co-Administered with MMR and Varicella Vaccines\***

	<b>Quadracel (N<sup>†</sup>=247-258)</b>	<b>DAPTACEL + IPOL (N<sup>†</sup>=248-253)</b>
<b>Anti-Poliovirus 1</b>		
% Booster Response <sup>‡</sup>	85.9 <sup>§</sup>	82.3
Pre-vaccination % ≥1:8 dilution	98.4	98.8
Post-vaccination % ≥1:8 dilution	100.0	99.6
Post-vaccination GMT	3,477 <sup>¶</sup>	2,731
<b>Anti-Poliovirus 2</b>		
% Booster Response <sup>‡</sup>	78.3 <sup>§</sup>	79.0
Pre-vaccination % ≥1:8 dilution	99.6	99.6
Post-vaccination % ≥1:8 dilution	100.0	100.0
Post-vaccination GMT	3,491 <sup>¶</sup>	3,894
<b>Anti-Poliovirus 3</b>		
% Booster Response <sup>‡</sup>	85.0 <sup>d</sup>	84.7
Pre-vaccination % ≥1:8 dilution	96.8	93.1
Post-vaccination % ≥1:8 dilution	100.0	100.0
Post-vaccination GMT	4,591 <sup>¶</sup>	3,419

\* ClinicalTrials.gov Identifier: NCT01346293.

<sup>†</sup> N = The number of subjects with available data.

<sup>‡</sup> Booster response: In subjects with pre-vaccination antibody concentrations <1:8 dilution, post-vaccination levels ≥1:8 dil; in subjects with pre-vaccination antibody concentrations ≥1:8 dilution, a 4-fold rise in post-vaccination antibody levels.

<sup>§</sup> Quadracel was non-inferior to DAPTACEL + IPOL based on the post-vaccination booster response rates for polio types 1, 2 and 3 (lower limits of the 2-sided 95% CIs of the difference [Quadracel minus DAPTACEL + IPOL] were > -10%).

<sup>¶</sup> Quadracel was non-inferior to DAPTACEL + IPOL based on the post-vaccination GMTs for polio types 1, 2 and 3 (lower limits of the 2-sided 95% CIs of the ratio [Quadracel / DAPTACEL + IPOL] were >2/3).



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## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

The vial stopper for this product is not made with natural rubber latex.

Quadracel is supplied in a single-dose vial (NDC No. 49281-564-58) in packages of 10 vials (NDC No.49281-564-10).

### 16.2 Storage and Handling

Quadracel should be stored at 2° to 8°C (35° to 46°F). Do not freeze. Product which has been exposed to freezing should not be used. Do not use after expiration date shown on the label.

## 17 PATIENT COUNSELING INFORMATION

Inform the parent or guardian of the following:

- The potential benefits and risks of immunization with Quadracel.
- The common adverse reactions that have occurred following administration of Quadracel or other vaccines containing similar components.
- Other adverse reactions can occur. Call healthcare provider with any adverse reactions of concern.

Provide the Vaccine Information Statements (VIS), which are required by the National Childhood Vaccine Injury Act of 1986.

Manufactured by:

**Sanofi Pasteur Limited**  
Toronto Ontario Canada

Distributed by:

**Sanofi Pasteur Inc.**

Swiftwater PA 18370 USA

Quadracel® is a registered trademark of Sanofi Pasteur Limited.

R0-1219 USA

SANOFI PASTEUR 

# **EXHIBIT 264**



## Package insert

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFLURIA safely and effectively. See full prescribing information for AFLURIA.

**AFLURIA, Influenza Vaccine**  
**Suspension for Intramuscular Injection**  
**2018-2019 Formula**  
**Initial U.S. Approval: 2007**

### RECENT MAJOR CHANGES

Indications and Usage (1) XX/2018  
Dosage and Administration (2) XX/2018

### INDICATIONS AND USAGE

- AFLURIA is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. (1)
- AFLURIA is approved for use in persons 6 months of age and older. (1)

### DOSAGE AND ADMINISTRATION

For intramuscular (IM) injection only, by needle and syringe (6 months and older) or by PharmaJet® Stratis® Needle-Free Injection System (18 through 64 years). (2)

Age	Dose	Schedule
6 through 35 months	One or two doses <sup>a</sup> , 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses <sup>a</sup> , 0.5mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5mL	Not Applicable

<sup>a</sup>1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines. (2)

### DOSAGE FORMS AND STRENGTHS

AFLURIA is a suspension for injection supplied in three presentations:

- 0.25 mL pre-filled syringe (single dose) (3, 11)
- 0.5 mL pre-filled syringe (single dose) (3, 11)
- 5 mL multi-dose vial (ten 0.5 mL doses) (3, 11)

### CONTRAINDICATIONS

- Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine. (4, 11)

### WARNINGS AND PRECAUTIONS

- If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA should be based on careful consideration of the potential benefits and risks. (5.1)
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. (5.2)

### ADVERSE REACTIONS

AFLURIA (trivalent formulation) administered by needle and syringe in children and adults:

- In children 5 through 17 years of age, the most common injection-site adverse reactions were pain ( $\geq 60\%$ ), redness ( $\geq 20\%$ ) and swelling ( $\geq 10\%$ ). The most common systemic adverse events were headache, myalgia ( $\geq 20\%$ ), irritability, malaise and fever ( $\geq 10\%$ ). (6.1)
- In adults 18 through 64 years of age, the most common injection-site adverse reactions were tenderness ( $\geq 60\%$ ), pain ( $\geq 40\%$ ), swelling ( $\geq 20\%$ ), and redness, itching ( $\geq 10\%$ ). The most common systemic adverse events were muscle aches ( $\geq 30\%$ ) and headache, malaise ( $\geq 20\%$ ). (6.1)
- In adults 65 years of age and older the most common injection-site adverse reactions were tenderness ( $\geq 30\%$ ) and pain ( $\geq 10\%$ ). No systemic adverse events occurred in  $\geq 10\%$  of subjects in this age group (6.1)

AFLURIA QUADRIVALENT (Influenza Vaccine), a four-strain version of AFLURIA administered by needle and syringe in children:

- In children 6 months through 35 months of age, the most commonly reported injection-site reactions were pain and redness ( $\geq 20\%$ ). The most common systemic adverse events were irritability ( $\geq 30\%$ ), diarrhea and loss of appetite ( $\geq 20\%$ ). (6.1)
- In children 36 through 59 months of age, the most commonly reported injection site reactions were pain ( $\geq 30\%$ ) and redness ( $\geq 20\%$ ). The most commonly reported systemic adverse events were malaise and fatigue and diarrhea ( $\geq 10\%$ ). (6.1)

AFLURIA administered by the PharmaJet Stratis Needle-Free Injection System:

- In adults 18 through 64 years of age, the most common injection-site adverse reactions when AFLURIA was administered by the PharmaJet® Stratis® Needle-Free Injection System up to 7 days post-vaccination were tenderness ( $\geq 80\%$ ), swelling, pain, redness ( $\geq 60\%$ ), itching ( $\geq 20\%$ ) and bruising ( $\geq 10\%$ ). The most common systemic adverse events within this period were myalgia, malaise ( $\geq 30\%$ ), and headache ( $\geq 20\%$ ). (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Seqirus at 1-855-358-8966 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).**

### USE IN SPECIFIC POPULATIONS

- The safety and effectiveness of AFLURIA in persons less than 6 months of age have not been established. (8.4)
- Antibody responses were lower in geriatric subjects than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2018



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### FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

AFLURIA<sup>®</sup> (Influenza Vaccine) is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. AFLURIA is approved for use in persons 6 months of age and older.

## 2 DOSAGE AND ADMINISTRATION

For intramuscular (IM) injection only, by needle and syringe (6 months of age and older) or by PharmaJet<sup>®</sup> Stratis<sup>®</sup> Needle-Free Injection System (18 through 64 years of age).

The dose and schedule for AFLURIA are presented in Table 1.

**Table 1: AFLURIA Dosage and Schedule**

Age	Dose	Schedule
6 months through 35 months	One or two doses <sup>a</sup> , 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One dose or two doses <sup>a</sup> , 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5mL	Not Applicable

<sup>a</sup> 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

Immediately before use, shake thoroughly and inspect visually. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever suspension and container permit. If either of these conditions exists, the vaccine should not be administered.

When using the single-dose pre-filled syringe, shake the syringe thoroughly and administer the dose immediately.

When using the multi-dose vial, shake the vial thoroughly before withdrawing each dose, and administer the dose immediately.

- Needle and Syringe: Draw up the exact dose using a separate sterile needle and syringe for each individual patient. It is recommended that small syringes (0.5 mL or 1 mL) be used to minimize any product loss.
- PharmaJet Stratis Needle-Free Injection System: For instructions on withdrawal of a 0.5 mL dose and use of the PharmaJet Stratis Needle-Free Injection System, refer to the Instructions For Use for the PharmaJet Stratis Needle-Free Injection System.

The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle



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of the upper arm if muscle mass is adequate) in persons 12 months through 35 months of age, or the deltoid muscle of the upper arm in persons  $\geq 36$  months of age.

Between uses, return the multi-dose vial to the recommended storage conditions between 2-8°C (36-46°F). **Do not freeze.** Discard if the vaccine has been frozen.

### 3 DOSAGE FORMS AND STRENGTHS

AFLURIA is a sterile suspension for intramuscular injection (*see Description [11]*).

AFLURIA is supplied in three presentations:

- 0.25 mL pre-filled syringe (single dose, for persons 6 months through 35 months of age)
- 0.5 mL pre-filled syringe (single dose, for persons 36 months of age and older).
- 5 mL multi-dose vial (for persons 6 months of age and older).

### 4 CONTRAINDICATIONS

AFLURIA is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine (*see Description [11]*).

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Guillain-Barré Syndrome

If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA should be based on careful consideration of the potential benefits and risks.

The 1976 swine influenza vaccine was associated with an increased frequency of GBS. Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than one additional case per 1 million persons vaccinated.

#### 5.2 Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

#### 5.3 Altered Immunocompetence

If AFLURIA is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

#### 5.4 Limitations of Vaccine Effectiveness

Vaccination with AFLURIA may not protect all individuals.





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### 6 ADVERSE REACTIONS

In children 5 through 17 years of age, the most common injection site reactions observed in clinical studies with AFLURIA administered by needle and syringe were pain ( $\geq 60\%$ ), redness ( $\geq 20\%$ ) and swelling ( $\geq 10\%$ ). The most common systemic adverse events were headache, myalgia ( $\geq 20\%$ ), irritability, malaise and fever ( $\geq 10\%$ ).

The safety experience with AFLURIA QUADRIVALENT (influenza vaccine), a four strain version of AFLURIA is relevant because both vaccines are manufactured using the same process and have overlapping compositions (see [Description \[11\]](#)).

In children 6 months through 35 months of age, the most frequently reported injection site reactions in a clinical study with AFLURIA QUADRIVALENT administered by needle and syringe were pain and redness ( $\geq 20\%$ ). The most common systemic adverse events were irritability ( $\geq 30\%$ ), diarrhea and loss of appetite ( $\geq 20\%$ ).

In children 36 through 59 months of age, the most frequently reported injection site reactions in a clinical study with AFLURIA QUADRIVALENT administered by needle and syringe were pain ( $\geq 30\%$ ) and redness ( $\geq 20\%$ ). The most commonly reported systemic adverse events were malaise and fatigue, and diarrhea ( $\geq 10\%$ ).

In adults 18 through 64 years of age, the most common injection-site adverse reactions observed in clinical studies with AFLURIA administered by needle and syringe were tenderness ( $\geq 60\%$ ), pain ( $\geq 40\%$ ), swelling ( $\geq 20\%$ ), redness and itching ( $\geq 10\%$ ). The most common systemic adverse events observed were muscle aches ( $\geq 30\%$ ), headache and malaise ( $\geq 20\%$ ).

In adults 65 years of age and older, the most common injection-site adverse reactions observed in clinical studies with AFLURIA administered by needle and syringe were tenderness ( $\geq 30\%$ ) and pain ( $\geq 10\%$ ). No systemic adverse reactions occurred in  $\geq 10\%$  of subjects in this age group.

In adults 18 through 64 years of age, using the PharmaJet Stratis Needle-Free Injection System, the most common injection-site adverse reactions observed in a clinical study with AFLURIA up to 7 days post-vaccination were tenderness ( $\geq 80\%$ ), swelling, pain, redness ( $\geq 60\%$ ), itching ( $\geq 20\%$ ) and bruising ( $\geq 10\%$ ). The most common systemic adverse events within this period were myalgia, malaise ( $\geq 30\%$ ) and headache ( $\geq 20\%$ ).

#### 6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a vaccine cannot be directly compared to rates in the clinical studies of another vaccine and may not reflect the rates observed in clinical practice.

##### *Children – AFLURIA*

In clinical studies, AFLURIA has been administered to, and safety information collected for, 3,009 children ages 6 months through 17 years. The exposure in children includes 1,601 aged 6 months to less than 5 years, 756 children ages 5 years to less than 9 years and 652 children ages

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98 9 years through 17 years. Clinical safety data for AFLURIA in children are presented from three  
99 clinical studies (Studies 1, 2 and 3). Data from a comparator-controlled trial (Study 1) are  
100 presented, followed by pooled data from two open label studies (Studies 2 and 3). Subjects 6  
101 months through 8 years of age received one or two vaccinations, administered by needle and  
102 syringe, as determined by previous vaccination history (for further details on clinical study design,  
103 dosing and demographics *see Clinical Studies [14]*).

104 Study 1 included 1,468 subjects for safety analysis, ages 6 months through 17 years, randomized  
105 to receive AFLURIA (735 subjects) or another U.S.-licensed trivalent inactivated influenza  
106 vaccine (manufactured by Sanofi Pasteur, Inc.) (733 subjects).

107 Study 2 included 1,976 subjects for safety analysis, ages 6 months through 17 years. All subjects  
108 received AFLURIA.

109 Study 3 included 298 subjects for safety analysis, ages 6 months through 8 years. All subjects  
110 received AFLURIA.

111 The safety assessment was similar for the three pediatric studies. Local (injection site) adverse  
112 reactions and systemic adverse events were solicited for 7 days post-vaccination (Tables 2 and  
113 3). Unsolicited adverse events were collected for 30 days post-vaccination. All adverse events  
114 are presented regardless of any treatment causality assigned by study investigators.

115 Among the pediatric studies, there were no vaccine-related deaths or vaccine-related serious  
116 adverse events reported in children 5 years of age and older.

117 In the comparator-controlled trial (Study 1), the rate of fever after the first dose of AFLURIA in  
118 subjects aged 5 through 8 years was 16% as compared to 8% in subjects who received the  
119 comparator. The rate of fever in subjects aged 9 through 17 years following a single dose of  
120 AFLURIA was 6% as compared to 4% in subjects who received the comparator. In all three  
121 pediatric studies, the rates of fever in subjects aged 5 through 8 years who received AFLURIA  
122 were lower after dose 2 than dose 1.

123 Data in Tables 2 and 3 are presented for children 5 years and older.



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**Table 2: Proportion of Subjects 5 through 17 Years of Age with Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of First or Second Dose of AFLURIA, Irrespective of Causality (Study 1)**

	Percentage <sup>a</sup> of Subjects in each Age Group Reporting Event			
	Subjects 5 through 8 years		Subjects 9 through 17 years	
	AFLURIA N=161 <sup>b</sup>	Comparator N=165 <sup>b</sup>	AFLURIA N=254 <sup>b</sup>	Comparator N=250 <sup>b</sup>
<b>After the First Dose</b>				
<b>Local Adverse Reactions</b>				
Pain	63	60	66	60
Redness	23	27	17	17
Induration	17	17	15	16
<b>Systemic Adverse Events</b>				
Myalgia	34	30	40	37
Malaise	24	13	22	20
Headache	21	19	27	26
Any Fever	16	8	6	4
Fever $\geq 102.2^{\circ}\text{F}$	5	1	3	1
Nausea/Vomiting	12	8	9	10
Diarrhea	7	7	8	10
	AFLURIA N=39 <sup>b</sup>	Comparator N=53 <sup>b</sup>		
<b>After the Second Dose</b>				
<b>Local Adverse Reactions</b>				
Pain	36	38	-	-
Redness	10	19	-	-
Induration	8	17	-	-
<b>Systemic Adverse Events</b>				
Diarrhea	13	6	-	-
Headache	13	13	-	-
Myalgia	13	17	-	-
Malaise	5	8	-	-
Nausea/Vomiting	3	8	-	-
Any Fever	0	2	-	-
Fever $\geq 102.2^{\circ}\text{F}$	0	0	-	-

<sup>a</sup> Proportion of subjects reporting each solicited local adverse reaction or systemic adverse event by treatment group based on the number of subjects contributing at least one data value for an individual sign/symptom (individual event denominators).

<sup>b</sup> N = number of subjects in the Safety Population for each treatment group.

**Table 3: Proportion of Subjects 5 through 17 Years of Age with Solicited Local Adverse Reactions or Systemic Adverse Events Within 7 Days after Administration of AFLURIA, Irrespective of Causality (Studies 2 and 3)**

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	Percentage <sup>a</sup> of Subjects in each Age Group Reporting Event		
	Studies 2 and 3 Subjects 5 through 8 years		Study 2 Subjects 9 through 17 years
	Dose 1 N=82-595 <sup>b</sup>	Dose 2 N=82-426 <sup>b</sup>	Dose 1 N=397 <sup>b</sup>
<b>Local Adverse Reactions</b>			
Pain	61	56	68
Erythema	24	23	17
Swelling	17	17	13
<b>Systemic Adverse Events</b>			
Irritability <sup>d</sup>	18	16	-
Headache	16	10	27
Malaise or feeling generally unwell <sup>c</sup>	16	8	17
Any Fever	13	6	5
Fever $\geq 102.2^{\circ}\text{F}$	3	2	1
General Muscle Ache (Myalgia)	12	8	20
Nausea/Vomiting <sup>c</sup>	7	3	5
Vomiting/Diarrhea <sup>d</sup>	5	6	-
Loss of appetite <sup>d</sup>	5	4	-
Diarrhea <sup>c</sup>	4	2	5

<sup>a</sup> Proportion of subjects reporting each solicited local adverse reaction or systemic adverse event by treatment group based on the number of subjects contributing at least one data value for an individual sign/symptom (individual event denominators).

<sup>b</sup> N = number of subjects in the Safety Population for each treatment group. Denominators for Dose 1 were: N=82 for Vomiting/Diarrhea, Irritability, Loss of appetite, N=513 for Malaise, Diarrhea, Nausea/Vomiting and N=593-595 for all other parameters. Denominators for Dose 2 were: N=82 for Vomiting/Diarrhea, Irritability, Loss of appetite, N=344 for Malaise, Diarrhea and Nausea/Vomiting and N=421-426 for all other parameters.

<sup>c</sup> These preferred terms were used to describe Solicited Adverse Events in Study 2.

<sup>d</sup> These preferred terms were used to describe Solicited Adverse Events in Study 3.

In Study 1, unsolicited adverse events that occurred in  $\geq 5\%$  of subjects 5 through 8 years following the first or second dose of AFLURIA included cough (15%) and pyrexia (9%). Unsolicited adverse events that occurred in  $\geq 5\%$  of subjects 9 through 17 years following a single dose of AFLURIA included cough (7%), oropharyngeal pain (7%), headache (7%) and nasal congestion (6%).

In Studies 2 and 3, unsolicited adverse events that occurred in  $\geq 5\%$  of subjects ages 5 years through 8 years after the first or second dose of AFLURIA included the following: upper respiratory tract infection (13%), cough (10%), rhinorrhea (7%), headache (5%), nasopharyngitis (5%) and pyrexia (5%). Unsolicited adverse events that occurred in  $\geq 5\%$  of subjects 9 through



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17 years following a single dose of AFLURIA included upper respiratory tract infection (9%) and headache (8%).

### ***Children 6 Months Through 59 Months of Age – AFLURIA QUADRIVALENT***

The safety experience with AFLURIA QUADRIVALENT (influenza vaccine), a four strain version of AFLURIA is relevant because both vaccines are manufactured using the same process and have overlapping compositions (see [Description \[11\]](#)). The safety of AFLURIA in children 6 through 59 months is based on a clinical trial conducted with AFLURIA QUADRIVALENT, Study 4, a randomized, observer-blind, comparator-controlled trial conducted in the U.S. in 2247 subjects aged 6 through 59 months. Subjects were stratified into one of two age cohorts of 6 through 35 months or 36 through 59 months (41.6% and 58.4% of the study population, respectively). The mean age of the population was 36.6 months, 51.6% were male, and racial groups consisted of 71.0% White, 21.5% Black, 1.1% Asian, 0.7% Native Hawaiian/Pacific Islander, and 0.3% American Indian/Native American; 26.4% of subjects were Hispanic/Latino. The mean ages of subjects 6 through 35 months and 36 through 59 months were 21.7 months and 47.1 months, respectively. Subjects in the safety population (N=2232) received either AFLURIA QUADRIVALENT (N=1673) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=559). Study subjects were scheduled to receive either a single vaccination or two vaccinations 28 days apart based on their previous vaccination history. In this study, AFLURIA QUADRIVALENT and comparator vaccine were administered by needle and syringe (see [Clinical Studies \[14\]](#)).

Local (injection site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination. Cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and swelling/lump) at the injection site were monitored for 28 days post-vaccination. Subjects were instructed to report and return to clinic within 24 hours in the event of a cellulitis-like reaction. Unsolicited adverse events were collected for 28 days post-vaccination, and SAEs for 6 months following the last vaccination. All solicited local adverse reactions and systemic adverse events following any vaccination (first or second dose) are presented in Table 4.



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**Table 4: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA QUADRIVALENT or Comparator QIV (Study 4) <sup>a</sup>**

	Percentage (%) <sup>b</sup> of Subjects in each Age Cohort Reporting an Event							
	6 through 35 months				36 through 59 months			
	AFLURIA Quadrivalent N= 668-669 <sup>c</sup>		Comparator N= 226-227 <sup>c</sup>		AFLURIA Quadrivalent N= 947-949 <sup>c</sup>		Comparator N= 317-318 <sup>c</sup>	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
<b>Local Adverse Reactions <sup>d</sup></b>								
Pain	20.8	0.1	25.6	0.4	35.5	0	31.4	0.6
Redness	20.8	0.6	17.6	1.8	22.4	2.3	20.8	5.3
Swelling/Lump	6.1	0.4	6.2	0.9	10.1	1.7	12.9	2.5
<b>Systemic Adverse Events <sup>e</sup></b>								
Irritability	32.9	0.7	28.2	0.4	-	-	-	-
Diarrhea	24.2	0.1	25.6	0.4	12.1	0.1	8.8	0.6
Loss of Appetite	20.0	0.3	19.4	0.4	-	-	-	-
Malaise and Fatigue	-	-	-	-	14.3	0.5	13.2	0.3
Myalgia	-	-	-	-	9.9	0.1	9.4	0
Nausea and/or vomiting	9.4	0.7	11.0	0	9.2	0.4	6.6	0.3
Headache	-	-	-	-	6.2	0.4	5.0	0
Fever <sup>f</sup>	7.2	2.5	11.9	2.6	4.8	1.2	6.0	0.9

Abbreviations: Gr 3, Grade 3 (severe); Comparator, Comparator quadrivalent influenza vaccine [Fluzone<sup>®</sup> Quadrivalent (Sanofi Pasteur)]

<sup>a</sup> NCT02914275

<sup>b</sup> Percent (%) is derived from the number of subjects that reported the event divided by the number of subjects in the Solicited Safety Population with non-missing data for each age cohort, treatment group, and each solicited parameter.

<sup>c</sup> N = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety data) for each study vaccine group.

<sup>d</sup> Local adverse reactions: Grade 3 pain is that which prevents daily activity (36 through 59 month subjects); or cried when limb was moved or spontaneously painful (6 through 35 month subjects); Swelling/Lump and redness: any =  $\geq$  0mm diameter, Grade 3 =  $\geq$  30mm diameter.

<sup>e</sup> Systemic adverse events: Fever: any =  $\geq$  99.5°F (Axillary), Grade 3 =  $\geq$  101.3°F (Axillary); Grade 3 for all other adverse events is that which prevents daily activity; Irritability, Loss of Appetite, Malaise and Fatigue, Myalgia and Headache are age specific systemic adverse events, where “-” denotes event was not applicable to that age cohort.

<sup>f</sup> Prophylactic antipyretics (acetaminophen or ibuprofen-containing medications) were not permitted. Antipyretics used to treat fever were permitted. The frequencies of antipyretic use in the seven days following any vaccination were as follows: 6 through 35 months (Afluria QIV 5.9%, Comparator QIV 9.0%); 36 through 59 months (Afluria QIV 3.7%, Comparator QIV 2.5%).

In subjects 6 through 35 months of age, all solicited local adverse reactions and systemic adverse events were reported at lower frequencies after the second vaccination than after the first vaccination with AFLURIA QUADRIVALENT.

In subjects 36 through 59 months of age, all solicited local adverse reactions and systemic adverse events were reported at lower frequencies after the second vaccination than after the first vaccination with AFLURIA QUADRIVALENT.





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The most commonly reported unsolicited adverse events in the 28 days following the first or second dose of AFLURIA QUADRIVALENT in subjects 6 through 35 months of age were rhinorrhea (11.2%), cough (10.4%), pyrexia (6.3%), upper respiratory tract infection (4.8%), diarrhea (3.7%), otitis media (2.4%), vomiting (2.4%), nasal congestion (2.4%), nasopharyngitis (1.9%), irritability (1.7%), ear infection (1.6%), croup infectious (1.4%), teething (1.3%), rash (1.2%), influenza like illness (1.0%) and fatigue (1.0%), and were similar to comparator.

The most commonly reported unsolicited adverse events in the 28 days following the first or second dose of AFLURIA QUADRIVALENT in subjects 36 through 59 months of age were cough (7.7%), rhinorrhea (4.9%), pyrexia (3.7%), upper respiratory tract infection (2.5%), vomiting (2.1%), nasal congestion (1.6%), nasopharyngitis (1.7%), oropharyngeal pain (1.2%) diarrhea (1.1%) and fatigue (1.1%), and were similar to the comparator.

No deaths were reported in Study 4. In the 180 days following vaccinations, AFLURIA QUADRIVALENT and comparator vaccine recipients experienced similar rates of serious adverse events (SAEs), none of which were related to study vaccines. No vaccine-related febrile seizures occurred in Study 4. Unrelated SAEs of febrile seizures occurred in two AFLURIA QUADRIVALENT recipients (6 through 35 months age group) at 43 and 104 days post-vaccinations.

#### **Adults – AFLURIA**

In clinical studies comparing AFLURIA to placebo or a comparator trivalent inactivated influenza vaccine, a single dose of AFLURIA was administered to, and safety information collected for, 11,104 subjects ages 18 through 64 years and 836 subjects ages 65 years and older. Clinical safety data for AFLURIA in adults are presented from three clinical studies (Studies 5 through 7) conducted in the U.S. and one clinical study (Study 8) conducted in the UK.

Study 5 included 1,357 subjects for safety analysis, ages 18 through 64 years, randomized to receive AFLURIA (1,089 subjects) or placebo (268 subjects) (*see Clinical Studies [14]*).

Study 6 included 15,020 subjects for safety analysis, ages 18 through 64 years, randomized to receive AFLURIA (10,015 subjects) or placebo (5,005 subjects) (*see Clinical Studies [14]*).

Study 7 included 1,266 subjects for safety analysis, ages 65 years and older, randomized to receive AFLURIA (630 subjects) or another U.S.-licensed trivalent inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.) as an active comparator (636 subjects) (*see Clinical Studies [14]*).

Study 8 included 275 subjects for safety analysis, ages 65 years and older, randomized to receive AFLURIA (206 subjects) or a UK-licensed trivalent inactivated influenza vaccine (manufactured by GSK) as an active comparator (69 subjects).

The safety assessment was identical for the four adult studies. Local (injection-site) adverse reactions and systemic adverse events were solicited for 5 days post-vaccination (Table 5, studies





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246 5 through 7). Unsolicited adverse events were collected for 21 days post-vaccination. All  
247 adverse events are presented regardless of any treatment causality assigned by study  
248 investigators.

249 Among adult studies, there were no vaccine-related deaths or vaccine-related serious adverse  
250 events reported.

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**Table 5: Proportion of Subjects 18 Years of Age and Older with Solicited Local Adverse Reactions or Systemic Adverse Events within 5 Days after Administration of AFLURIA or Placebo, Irrespective of Causality (Studies 5, 6 and 7)**

	Percentage <sup>a</sup> of Subjects in each Age Group Reporting Event					
	Study 5 Subjects 18 through 64 years		Study 6 Subjects 18 through 64 years		Study 7 Subjects ≥ 65 years	
	AFLURIA N=1087-1088 <sup>b</sup>	Placebo N=266 <sup>b</sup>	AFLURIA N=10,015 <sup>b</sup>	Placebo N=5005 <sup>b</sup>	AFLURIA N=630 <sup>b</sup>	Comparator N=636 <sup>b</sup>
<b>Local Adverse Reactions</b>						
Tenderness (Pain on touching)	60	18	69	17	36	31
Pain (without touching)	40	9	48	11	15	14
Redness	16	8	4	<1	3	1
Swelling	9	1	4	<1	7	8
Bruising	5	1	1	1	<1	1
<b>Systemic Adverse Events</b>						
Headache	26	26	25	23	9	11
Malaise	19	19	29	26	7	6
Muscle aches	13	9	21	12	9	8
Nausea	6	9	7	6	2	1
Chills/Shivering	3	2	5	4	2	2
Fever	1	1	3	2	<1	1

<sup>a</sup> Proportion of subjects reporting each solicited local adverse reaction or systemic adverse event by treatment group based on the number of subjects contributing at least one data value for an individual sign/symptom (individual event denominators).

<sup>b</sup> N = number of subjects in the Safety Population for each treatment group.

In Study 5, headache was the only unsolicited adverse event that occurred in ≥ 5% of subjects who received AFLURIA or placebo (8% versus 6%, respectively).

In Study 6, unsolicited adverse events that occurred in ≥ 5% of subjects who received AFLURIA or placebo included headache (AFLURIA 12%, placebo 11%) and oropharyngeal pain (AFLURIA 5%, placebo 5%).

In Study 7, headache was the only unsolicited adverse event that occurred in ≥ 5% of subjects who received AFLURIA (5%).

Studies 1 to 8 were all conducted when AFLURIA and AFLURIA QUADRIVALENT were administered by needle and syringe.

Additionally, safety information has been collected in a clinical study of AFLURIA administered using the PharmaJet Stratis Needle-Free Injection System (Study 9). Study 9 included 1,247 subjects for safety analysis, ages 18 through 64 years, randomized to receive AFLURIA by either the PharmaJet Stratis Needle-Free Injection System (624 subjects) or needle and syringe (623 subjects). No deaths or vaccine-related serious adverse events were reported in Study 7. Local

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(injection-site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination (Table 6).

**Table 6: Proportion of Subjects 18 through 64 Years of Age with Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA by PharmaJet Stratis Needle-Free Injection System or Needle and Syringe Irrespective of Causality (Study 9).**

	Percentage <sup>a</sup> of Subjects Reporting Event	
	Study 9	
	Subjects 18 through 64 years	
	AFLURIA	
	PharmaJet Stratis Needle-Free Injection System N=540-616 <sup>b</sup>	Needle and Syringe N=599-606 <sup>b</sup>
<b>Local Adverse Reactions</b>		
Tenderness	89	78
Swelling	65	20
Pain	64	49
Redness	60	19
Itching <sup>c</sup>	28	10
Bruising	18	5
<b>Systemic Adverse Events</b>		
Myalgia	36	36
Malaise	31	28
Headache	25	22
Chills	7	7
Nausea	7	7
Vomiting	1	2
Fever	0	0

<sup>a</sup> Proportion of subjects reporting each local adverse reaction or systemic adverse event by treatment group based on the number of subjects contributing at least one data value for an individual sign/symptom (individual event denominators).

<sup>b</sup> N = number of subjects in the Safety Population for each treatment group. Denominators for the PharmaJet Stratis Needle-Free Injection System group were: N=540 for itching and N=605-616 for all other parameters. Denominators for the needle and syringe group were: N=527 for itching and N=599-606 for all other parameters.

<sup>c</sup> A total of 155 subjects (approximately randomly distributed between PharmaJet Stratis Needle-Free Injection System and needle and syringe groups) received Diary Cards without itching listed as a solicited symptom.

In Study 9, no unsolicited adverse events occurred in  $\geq 5\%$  of subjects who received AFLURIA administered by PharmaJet Stratis Needle-Free Injection System up to 28 days post-vaccination.

## 6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal



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relationship to vaccine exposure. The adverse reactions described have been included in this section because they: 1) represent reactions that are known to occur following immunizations generally or influenza immunizations specifically; 2) are potentially serious; or 3) have been reported frequently. These adverse reactions reflect experience in both children and adults and include those identified during post-approval use of AFLURIA outside the U.S. since 1985.

### **Blood and lymphatic system disorders**

Thrombocytopenia

### **Immune system disorders**

Allergic or immediate hypersensitivity reactions including anaphylactic shock and serum sickness

### **Nervous system disorders**

Neuralgia, paresthesia, convulsions (including febrile seizures), encephalomyelitis, encephalopathy, neuritis or neuropathy, transverse myelitis, and GBS

### **Vascular disorders**

Vasculitis which may be associated with transient renal involvement

### **Skin and subcutaneous tissue disorders**

Pruritus, urticaria, and rash

### **General disorders and administration site conditions**

Cellulitis and large injection site swelling

Influenza-like illness

## **6.3 Adverse Reactions Associated With Influenza Vaccination**

Anaphylaxis has been reported after administration of AFLURIA. Egg protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, asthma, and systemic anaphylaxis (*see [Contraindications \[4\]](#)*).

Neurological disorders temporally associated with influenza vaccination, such as encephalopathy, optic neuritis/neuropathy, partial facial paralysis, and brachial plexus neuropathy, have been reported.

Microscopic polyangiitis (vasculitis) has been reported temporally associated with influenza vaccination.

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**7 DRUG INTERACTIONS****7.1 Concurrent Use With Other Vaccines**

There are no data to assess the concomitant administration of AFLURIA with other vaccines. If AFLURIA is given at the same time as another injectable vaccine(s), the vaccine(s) should be administered in separate syringes and a separate arm should be used.

AFLURIA should not be mixed with any other vaccine in the same syringe or vial.

**8 USE IN SPECIFIC POPULATIONS****8.1 Pregnancy**Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are insufficient data for AFLURIA in pregnant women to inform vaccine-associated risks in pregnancy. A developmental toxicity study has been performed in female rats administered AFLURIA prior to mating and during gestation. A single human dose (0.5 mL, divided) was injected on each occasion. This study revealed no evidence of harm to the fetus due to AFLURIA ([see 8.1 Pregnancy -Data](#)).

Clinical Considerations*Disease-associated Maternal and/or Embryo-Fetal Risk*

Pregnant women are at increased risk for severe illness due to influenza compared to non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data*Animal Data*

In a developmental toxicity study, female rats were administered a single human dose [0.5 mL (divided)] of AFLURIA by intramuscular injection 21 days and 7 days prior to mating, and on gestation day 6. Some rats were administered an additional dose on gestation day 20. No vaccine-related fetal malformations or variations and no adverse effects on pre-weaning development were observed in the study.

**8.2 Lactation**Risk Summary

It is not known whether AFLURIA is excreted in human milk. Data are not available to assess the effects of AFLURIA on the breastfed infant or on milk production/excretion.



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The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AFLURIA and any potential adverse effects on the breastfed child from AFLURIA or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

**8.4 Pediatric Use**

The safety and effectiveness of AFLURIA in persons less than 6 months of age have not been established.

The PharmaJet Stratis Needle-Free Injection System is not approved as a method of administering AFLURIA to children and adolescents less than 18 years of age due to lack of adequate data supporting safety and effectiveness in this population.

**8.5 Geriatric Use**

In clinical studies, AFLURIA has been administered to, and safety information collected for, 836 subjects ages 65 years and older (*see Clinical Trials Experience [6.1]*). After administration of AFLURIA, hemagglutination-inhibiting antibody responses in persons 65 years of age and older were lower as compared to younger adult subjects (*see Clinical Studies [14]*).

The PharmaJet Stratis Needle-Free Injection System is not approved as a method of administering AFLURIA to adults 65 years of age and older due to lack of adequate data supporting safety and effectiveness in this population.

**11 DESCRIPTION**

AFLURIA, Influenza Vaccine for intramuscular injection, is a sterile, clear, colorless to slightly opalescent suspension with some sediment that resuspends upon shaking to form a homogeneous suspension. AFLURIA is prepared from influenza virus propagated in the allantoic fluid of embryonated chicken eggs. Following harvest, the virus is purified in a sucrose density gradient using continuous flow zonal centrifugation. The purified virus is inactivated with beta-propiolactone, and the virus particles are disrupted using sodium taurodeoxycholate to produce a "split virion". The disrupted virus is further purified and suspended in a phosphate buffered isotonic solution.

AFLURIA is standardized according to USPHS requirements for the 2018-2019 influenza season and is formulated to contain 45 mcg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA for each of the three influenza strains recommended for the 2018-2019 Northern Hemisphere influenza season: A/Singapore/GP1908/2015 IVR 180A (H1N1) (an A/Michigan/45/2015 – like virus), A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2) (an A/Singapore/INFIMH-16-0019/2016 – like virus) and B/Maryland/15/2016 (a B/Colorado/06/2017 – like virus). A 0.25 mL dose contains 7.5 mcg HA of each of the same three influenza strains.

Thimerosal, a mercury derivative, is not used in the manufacturing process for the single dose presentations; therefore these products contain no preservative. The multi-dose presentation



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contains thimerosal, added as a preservative; each 0.5 mL dose contains 24.5 mcg of mercury and each 0.25 mL dose contains 12.25 mcg of mercury.

A single 0.5 mL dose of AFLURIA contains sodium chloride (4.1 mg), monobasic sodium phosphate (80 mcg), dibasic sodium phosphate (300 mcg), monobasic potassium phosphate (20 mcg), potassium chloride (20 mcg), and calcium chloride (0.5 mcg). From the manufacturing process, each 0.5 mL dose may also contain residual amounts of sodium taurodeoxycholate ( $\leq 10$  ppm), ovalbumin ( $< 1$  mcg), sucrose ( $< 10$  mcg), neomycin sulfate ( $\leq 61.5$  nanograms [ng]), polymyxin B ( $\leq 10.5$  ng), and beta-propiolactone ( $\leq 2$  ng). A single 0.25 mL dose of AFLURIA contains half of these quantities.

The rubber tip cap and plunger used for the preservative-free, single-dose syringes and the rubber stoppers used for the multi-dose vial were not made with natural rubber latex.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977 antigenic variants of influenza A (H1N1 and H3N2) and influenza B viruses have been in global circulation. Specific levels of hemagglutination inhibition (HI) antibody titers post-vaccination with inactivated influenza vaccine have not been correlated with protection from influenza virus. In some human studies, antibody titers of 1:40 or greater have been associated with protection from influenza illness in up to 50% of subjects.<sup>2,3</sup>

Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual change to one or more new strains in each year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the HA of three strains (i.e., typically two type A and one type B) representing the influenza viruses likely to be circulating in the U.S. during the upcoming winter.

Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination and circulating strains of influenza virus change from year to year.<sup>1</sup>

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

AFLURIA has not been evaluated for carcinogenic or mutagenic potential, or male infertility in animals. A reproductive study of female rats vaccinated with AFLURIA revealed no impairment of fertility (see Pregnancy, 8.1).



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**14 CLINICAL STUDIES****14.1 Efficacy of AFLURIA Against Laboratory-Confirmed Influenza**

In Study 6, the efficacy of AFLURIA was demonstrated in a randomized, observer-blind, placebo-controlled study conducted in 15,044 subjects. Healthy subjects 18 through 64 years of age were randomized in a 2:1 ratio to receive a single dose of AFLURIA (enrolled subjects: 10,033; evaluable subjects: 9,889) or placebo (enrolled subjects: 5,011; evaluable subjects: 4,960). The mean age of all randomized subjects was 35.5 years. 54.4% were female and 90.2% were White. Laboratory-confirmed influenza was assessed by active and passive surveillance of influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of the influenza season, approximately 6 months post-vaccination. ILI was defined as at least one respiratory symptom (e.g., cough, sore throat, nasal congestion) and at least one systemic symptom (e.g., oral temperature of 100.0°F or higher, feverishness, chills, body aches). Nasal and throat swabs were collected from subjects who presented with an ILI for laboratory confirmation by viral culture and real-time reverse transcription polymerase chain reaction. Influenza virus strain was further characterized using gene sequencing and pyrosequencing.

Attack rates and vaccine efficacy, defined as the relative reduction in the influenza infection rate for AFLURIA compared to placebo, were calculated using the per protocol population. Vaccine efficacy against laboratory-confirmed influenza infection due to influenza A or B virus strains contained in the vaccine was 60% with a lower limit of the 95% CI of 41% (Table 7).



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**Table 7: Laboratory-Confirmed Influenza Infection Rate and Vaccine Efficacy in Adults 18 through 64 Years of Age (Study 6)**

	Subjects <sup>a</sup>	Laboratory-Confirmed Influenza Cases	Influenza Infection Rate	Vaccine Efficacy <sup>b</sup>	
	N	N	n/N %	%	Lower Limit of the 95% CI
Vaccine-matched Strains					
AFLURIA	9889	58	0.59	60	41
Placebo	4960	73	1.47		
Any Influenza Virus Strain					
AFLURIA	9889	222	2.24	42	28
Placebo	4960	192	3.87		

Abbreviations: CI, confidence interval

<sup>a</sup> The Per Protocol Population was identical to the Evaluable Population in this study.

<sup>b</sup> Vaccine efficacy = 1 minus the ratio of AFLURIA/placebo infection rates. The objective of the study was to demonstrate that the lower limit of the CI for vaccine efficacy was greater than 40%.

## 14.2 Immunogenicity of AFLURIA in Children 5 through 17 Years Administered by Needle and Syringe

Study 1 was a randomized, observer-blind, comparator-controlled study to evaluate the immunological non-inferiority of AFLURIA to a U.S.-licensed trivalent inactivated influenza vaccine (manufactured by Sanofi Pasteur, Inc.) in subjects 6 months through 17 years of age. Study vaccines were administered by needle and syringe. Results are presented for children 5 through 17 years of age (Table 8). A total of 832 subjects (aged 5 through 17 years) were enrolled. Subjects were randomized in a 1:1 ratio to receive AFLURIA (enrolled subjects: 417; evaluable subjects: 383) or the comparator vaccine (enrolled subjects: 415; evaluable subjects: 383).

Children 6 months through 8 years of age with no history of influenza vaccination received 2 doses approximately 28 days apart. Children 6 months through 8 years of age with a history of influenza vaccination and children 9 years of age and older received 1 dose. Children 6 months through 35 months of age received 0.25 mL of AFLURIA or comparator influenza vaccine, and children 3 years of age and older received 0.5 mL of AFLURIA or comparator influenza vaccine. Nearly equal proportions of subjects were male (49.9%) and female (50.1%), and the majority were White (85.0%) or Black (10.3%).

Immunogenicity assessments were performed prior to vaccination and at 30 days after vaccination. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers) and the difference in seroconversion rates for each vaccine strain 21 days after the final vaccination. Pre-specified non-inferiority criteria required that the upper bound



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of the 2-sided 95% CI of the GMT ratio (Comparator/AFLURIA) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator minus AFLURIA) did not exceed 10.0% for each strain. As shown in Table 8, non-inferiority of AFLURIA to the comparator vaccine was demonstrated in the per protocol population for influenza A subtypes A(H1N1) and A(H3N2), but not for influenza type B. For influenza type B, non-inferiority was demonstrated for HI GMTs, but not for seroconversion rates. Note that the study was powered to assess the pre-specified non-inferiority criteria based on 1400 evaluable subjects. Analysis of the 761 subjects aged 5 through 17 years reduced the power of the study and widened the confidence intervals. In the pre-specified analysis, AFLURIA was not inferior to the comparator vaccine for all three virus strains. Post-hoc analyses of immunogenicity by gender did not demonstrate significant differences between males and females. The study was not sufficiently diverse to assess differences between races or ethnicities.

**Table 8: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA to a U.S.-Licensed Comparator, Subjects 5 through 17 Years of Age (Study 1)**

	Post-vaccination GMT		GMT Ratio <sup>a</sup>	Seroconversion % <sup>b</sup>		Difference	Met both pre-defined non-inferiority criteria? <sup>c</sup>
Strain	Comparator N=381	AFLURIA N=380	Comparator over AFLURIA (95% CI)	Comparator N=381	AFLURIA N=380	Comparator minus AFLURIA (95% CI)	
A(H1N1)	526.2	507.4	1.03 (0.88, 1.21)	62.7	62.6	0.1 (-6.8, 7.0)	Yes
A(H3N2)	1060.0	961.3	1.07 (0.94, 1.23)	72.2	69.7	2.4 (-4.0, 8.9)	Yes
B	123.3	110.1	1.10 (0.94, 1.29)	75.1	70.0	5.1 (-1.3, 11.4)	No

Abbreviations: CI, confidence interval; GMT, geometric mean titer.

<sup>a</sup> GMT ratios are adjusted for baseline HI titers

<sup>b</sup> Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer  $\geq 1:10$  or an increase in titer from  $< 1:10$  to  $\geq 1:40$ .

<sup>c</sup> Note that the study was powered to assess the pre-specified non-inferiority criteria based on 1400 evaluable subjects.

### 14.3 Immunogenicity of AFLURIA QUADRIVALENT in Children 6 months through 59 months of age Administered by Needle and Syringe

Data have also been collected in a clinical study of AFLURIA QUADRIVALENT, which is relevant to AFLURIA because both vaccines are manufactured using the same process and have overlapping compositions (Study 4).

Study 4 was a randomized, observer-blind, comparator-controlled trial conducted in the U.S. in children 6 months through 59 months of age. A total of 2247 subjects were randomized 3:1 to receive AFLURIA QUADRIVALENT (N=1684) or a U.S.-licensed comparator quadrivalent

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influenza vaccine (N=563). Children 6 months through 35 months received one or two 0.25 mL doses and children 36 months through 59 months received one or two 0.5 mL doses. Subjects were eligible to receive a second dose at least 28 days after the first dose depending on their influenza vaccination history, consistent with the 2016-2017 recommendations of the Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal Influenza with Vaccines. Approximately 40% of subjects in each treatment group received two vaccine doses.

Baseline serology for HI assessment was collected prior to vaccination. Postvaccination immunogenicity was evaluated by HI assay on sera obtained 28 days after the last vaccination dose.

The primary objective was to demonstrate that vaccination with AFLURIA QUADRIVALENT elicits an immune response that is not inferior to that of a comparator vaccine containing the same recommended virus strains. The Per Protocol Population (AFLURIA QUADRIVALENT n=1456, Comparator QIV n=484) was used for the primary endpoint analyses. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (Comparator QIV/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator QIV minus AFLURIA QUADRIVALENT) did not exceed 10.0% for each strain. Serum HI antibody responses to AFLURIA QUADRIVALENT were non-inferior for both GMT ratio and seroconversion rates relative to the comparator vaccine for all influenza strains (Table 9). Analyses of immunogenicity endpoints by gender did not demonstrate meaningful differences between males and females. The study population was not sufficiently diverse to assess differences among races or ethnicities.



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**Table 9: Post-Vaccination HI Antibody GMTs, SCR, and Analyses of Non-Inferiority of AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator Quadrivalent Influenza Vaccine for each Strain 28 Days after Last Vaccination Among a Pediatric Population 6 through 59 Months of Age (Per Protocol Population) (Study 4)<sup>a, b</sup>**

Strain	Post-vaccination GMT		GMT Ratio <sup>c</sup>	Seroconversion % <sup>d</sup>		SCR Difference <sup>e</sup>	Met both pre-defined non-inferiority criteria? <sup>f</sup>
	AFLURIA Quadrivalent N=1456	Comparator N=484	Comparator over AFLURIA Quadrivalent (95% CI)	AFLURIA Quadrivalent N=1456 (95% CI)	Comparator N=484 (95% CI)	Comparator minus AFLURIA Quadrivalent (95% CI)	
A(H1N1)	353.5 (n=1455 <sup>g</sup> )	281.0 (n=484)	0.79 (0.72, 0.88)	79.1 (76.9, 81.1) (n=1456)	68.8 (64.5, 72.9) (n=484)	-10.3 (-15.4, -5.1)	Yes
A(H3N2)	393.0 (n=1454 <sup>g</sup> )	500.5 (n=484)	1.27 (1.15, 1.42)	82.3 (80.2, 84.2) (n=1455 <sup>i</sup> )	84.9 (81.4, 88.0) (n=484)	2.6 (-2.5, 7.8)	Yes
B/Phuket/3073/2013 (B Yamagata)	23.7 (n=1455 <sup>g</sup> )	26.5 (n=484)	1.12 (1.01, 1.24)	38.9 (36.4, 41.4) (n=1456)	41.9 (37.5, 46.5) (n=484)	3.1 (-2.1, 8.2)	Yes
B/Brisbane/60/2008 (B Victoria)	54.6 (n=1455 <sup>g</sup> )	52.9 (n=483 <sup>h</sup> )	0.97 (0.86, 1.09)	60.2 (57.6, 62.7) (n=1456)	61.1 (56.6, 65.4) (n=483 <sup>h</sup> )	0.9 (-4.2, 6.1)	Yes

Abbreviations: CI, confidence interval; Comparator, Comparator quadrivalent influenza vaccine (Fluzone Quadrivalent [Sanofi Aventis]); GMT (adjusted), geometric mean titer; SCR, seroconversion rate.

<sup>a</sup> NCT02914275

<sup>b</sup> The Per-Protocol Population comprised all subjects (6 through 35 months of age receiving one or two 0.25 mL doses and 36 through 59 months of age receiving one or two 0.5 mL doses) in the Evaluable Population who did not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results.

<sup>c</sup> GMT Ratio = Comparator / AFLURIA QUADRIVALENT. Adjusted analysis model: Log-transformed Post-Vaccination HI Titer=Vaccine + Age Cohort [6 through 35 months or 36 through 59 months] + Gender + Vaccination History [y/n] + Log-transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Cohort\*Vaccine. The Age Cohort\*Vaccine interaction term was excluded from the model fit for the strains A(H1N1), A(H3N2) and B/Yamagata as the interaction result was non-significant (p>0.05). Least square means were back transformed.

<sup>d</sup> Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.

<sup>e</sup> Seroconversion rate difference = Comparator SCR percentage minus AFLURIA QUADRIVALENT SCR percentage.

<sup>f</sup> Noninferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator / AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95% CI on the difference between SCR Comparator– AFLURIA QUADRIVALENT should not exceed 10%.

<sup>g</sup> Subject 8400402-0073 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio

because the subject did not have information on all covariates (unknown prevaccination history).

<sup>h</sup> Subject 8400427-0070 had missing B/Victoria Antigen pre-vaccination titer.

<sup>i</sup> Subject 8400402-0074 had missing A/H3N2 post-vaccination titer.

## 14.4 Immunogenicity of AFLURIA in Adults and Older Adults Administered by Needle and Syringe

Two randomized, controlled clinical studies of AFLURIA evaluated the immune responses by measuring HI antibody titers to each virus strain in the vaccine in adults as compared to placebo (adults 18 through 64 years) or another U.S.-licensed trivalent influenza vaccine (adults ≥ 65 years). In these studies, post-vaccination immunogenicity was evaluated on sera obtained 21 days after administration of a single dose of AFLURIA.



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Study 5 was a randomized, double-blinded, placebo-controlled, multi-center study in healthy subjects ages 18 through 64 years. A total of 1,357 subjects were vaccinated [1,089 subjects with AFLURIA and 268 with a placebo]. Subjects who received AFLURIA were vaccinated using either the preservative-free or thimerosal-containing presentation. The evaluable population consisted of 1,341 subjects [1,077 in the AFLURIA group and 264 in the placebo group]. The mean age of the entire evaluable population receiving AFLURIA was 38 years. 62.5% of subjects were female, 81.3% were White, 12.1% were Black, and 6.2% were Asian.

Serum HI antibody responses to AFLURIA met the pre-specified co-primary endpoint criteria for all three virus strains (Table 10). Similar responses were observed between genders. The study was not sufficiently diverse to assess immunogenicity by race or ethnicity.

**Table 10: Serum Antibody Responses in Subjects 18 through 64 Years of Age Receiving AFLURIA (Study 5)**

Strain Variable	AFLURIA N=1077 value (95% CI)	Placebo N=264 value (95% CI)
<b>A(H1N1)</b>		
HI Titer $\geq 1:40$ <sup>a</sup>	97.8% (96.7, 98.6)	74.6% (68.9, 79.8)
Seroconversion Rate (%) <sup>b</sup>	48.7% (45.6, 51.7)	2.3% (0.8, 4.9)
<b>A(H3N2)</b>		
HI Titer $\geq 1:40$ <sup>a</sup>	99.9% (99.5, 100.0)	72.0% (66.1, 77.3)
Seroconversion Rate (%) <sup>b</sup>	71.5% (68.7, 74.2)	0.0% (N/A)
<b>B</b>		
HI Titer $\geq 1:40$ <sup>a</sup>	94.2% (92.7, 95.6)	47.0% (40.8, 53.2)
Seroconversion Rate (%) <sup>b</sup>	69.7% (66.9, 72.5)	0.4% (< 0.1, 2.1)

<sup>a</sup> HI titer  $\geq 1:40$  is defined as the proportion of subjects with a minimum post-vaccination HI antibody titer of 1:40. Lower bound of 95% CI for HI antibody titer  $\geq 1:40$  should be  $> 70\%$  for the study population.

<sup>b</sup> Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer  $\geq 1:10$  or an increase in titer from  $< 1:10$  to  $\geq 1:40$ . Lower bound of 95% CI for seroconversion should be  $> 40\%$  for the study population.

Study 7 was a randomized, observer-blind, comparator-controlled study that enrolled 1,268 subjects 65 years of age and older (Table 11). This study compared the immune response following administration of AFLURIA to that following a U.S.-licensed trivalent inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.). Subjects were randomized in a 1:1 ratio to receive a single vaccination of AFLURIA (enrolled subjects: 631; evaluable subjects: 605) or the comparator vaccine (enrolled subjects: 637; evaluable subjects: 610). Immunogenicity assessments were performed prior to vaccination and at 21 days after vaccination. Most of the subjects in the per-protocol immunogenicity population were female (56.7%) and White (97.4%). 2.0% were Black and less than 1.0% were of other races or ethnicities.





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The co-primary endpoints were HI GMT ratios (adjusted for baseline HI titers) and the difference in seroconversion rates for each vaccine strain 21 days after vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (Comparator/AFLURIA) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator minus AFLURIA) did not exceed 10.0% for each strain. As shown in Table 11, non-inferiority of AFLURIA to the comparator vaccine was demonstrated in the per protocol population for influenza A subtypes A(H1N1) and A(H3N2), but not for influenza type B. For the B strain, non-inferiority was demonstrated for HI GMTs, but not for seroconversion rates. Post-hoc analyses of immunogenicity by gender did not demonstrate significant differences between males and females. The study was not sufficiently diverse to assess differences between races or ethnicities.

**Table 11: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA to a U.S. Licensed Comparator, Adults 65 Years of Age and Older (Study 7)**

Strain	Post-vaccination GMT		GMT Ratio <sup>a</sup>	Seroconversion % <sup>b</sup>		Difference	Met both pre-defined non-inferiority criteria?
	Comparator N=610	AFLURIA N=605	Comparator over AFLURIA (95% CI)	Comparator N=610	AFLURIA N=605	Comparator minus AFLURIA (95% CI)	
A(H1N1)	59.2	59.4	1.04 (0.92, 1.18)	43.0	38.8	4.1 (-1.4, 9.6)	Yes
A(H3N2)	337.7	376.8	0.95 (0.83, 1.08)	68.7	69.4	-0.7 (-5.9, 4.5)	Yes
B	33.4	30.4	1.12 (1.01, 1.25)	34.4	29.3	5.2 (-0.1, 10.4)	No

Abbreviations: CI, confidence interval; GMT, geometric mean titer.

<sup>a</sup> Post-vaccination GMTs were adjusted for baseline HI titers.

<sup>b</sup> Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer  $\geq 1:10$  or an increase in titer from  $< 1:10$  to  $\geq 1:40$ .

### 14.5 Immunogenicity of AFLURIA in Adults Administered by PharmaJet Stratis Needle-Free Injection System

Study 9 was a randomized, comparator-controlled non-inferiority study that enrolled 1,250 subjects 18 through 64 years of age. This study compared the immune response following administration of AFLURIA when delivered IM using either the PharmaJet Stratis Needle-Free Injection System or needle and syringe. Immunogenicity assessments were performed prior to vaccination and at 28 days after vaccination in the immunogenicity population (1,130 subjects, 562 PharmaJet Stratis Needle-Free Injection System group, 568 needle and syringe group). The co-primary endpoints were HI GMT ratios for each vaccine strain and the absolute difference in seroconversion rates for each vaccine strain 28 days after vaccination. As shown in Table 12, non-inferiority of administration of AFLURIA by the PharmaJet Stratis Needle-Free Injection System compared to administration of AFLURIA by needle and syringe was demonstrated in





## Package insert

the immunogenicity population for all strains. Post-hoc analyses of immunogenicity by age showed that younger subjects (18 through 49 years) elicited higher immunological responses than older subjects (50 through 64 years). Post-hoc analyses of immunogenicity according to gender and body mass index did not reveal significant influences of these variables on immune responses. The study population was not sufficiently diverse to assess immunogenicity by race or ethnicity.

**Table 12: Baseline and Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA Administered by PharmaJet Stratis Needle-Free Injection System or Needle and Syringe, Adults 18 through 64 Years of Age (Study 9)**

	Baseline GMT		Post-vaccination GMT		GMT Ratio <sup>a</sup>	Seroconversion % <sup>b</sup>		Difference	
Strain	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe over PharmaJet Stratis Needle-Free Injection System (95% CI)	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe minus PharmaJet Stratis Needle-Free Injection System (95% CI)	Met both pre-defined non-inferiority criteria? <sup>c</sup>
A(H1N1)	79.5	83.7	280.6	282.9	0.99 (0.88, 1.12)	38.4	37.5	0.8 (-4.8, 6.5)	Yes
A(H3N2)	75.4	68.1	265.9	247.3	1.08 (0.96, 1.21)	45.1	43.8	1.3 (-4.5, 7.1)	Yes
B	12.6	13.5	39.7	42.5	0.94 (0.83, 1.06)	35.2	34.9	0.3 (-5.2, 5.9)	Yes

Abbreviations: CI, confidence interval; GMT, geometric mean titer

<sup>a</sup> GMT ratio is defined as post-vaccination GMT for Needle and Syringe/PharmaJet Stratis Needle-Free Injection System

<sup>b</sup> Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer  $\geq 1:10$  or an increase in titer from  $< 1:10$  to  $\geq 1:40$ .

<sup>c</sup> Non-inferiority (NI) criteria for the GMT ratio: upper bound of 2-sided 95% CI on the ratio of Needle and Syringe/PharmaJet Stratis Needle-Free Injection System. GMT should not exceed 1.5. NI criteria for the seroconversion rate (SCR) difference: upper bound of 2-sided 95% CI on the difference between SCR Needle and Syringe – SCR PharmaJet Stratis Needle-Free Injection System should not exceed 10%.

## 15 REFERENCES

- Centers for Disease Control and Prevention. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2010;59 (RR-8):1-62.
- Hannoun C, Megas F, Piercy J. Immunogenicity and Protective Efficacy of Influenza Vaccination. *Virus Res* 2004;103:133-138.



## Package insert

3. Hobson D, Curry RL, Beare AS, et al. The Role of Serum Hemagglutination-Inhibiting Antibody in Protection against Challenge Infection with Influenza A2 and B Viruses. *J Hyg Camb* 1972;70:767-777.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

Each product presentation includes a package insert and the following components:

Presentation	Carton NDC Number	Components
Pre-Filled Syringe	33332-518-20	<ul style="list-style-type: none"> <li>Ten 0.25 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-518-21]</li> </ul>
Pre-Filled Syringe	33332-018-01	<ul style="list-style-type: none"> <li>Ten 0.5 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-018-02]</li> </ul>
Multi-Dose Vial	33332-118-10	<ul style="list-style-type: none"> <li>One 5 mL vial, which contains ten 0.5 mL doses [NDC 33332-118-11]</li> </ul>

### 16.2 Storage and Handling

- Store refrigerated at 2–8°C (36–46°F).
- Do not freeze. Discard if product has been frozen.
- Protect from light.
- Do not use AFLURIA beyond the expiration date printed on the label.
- Once the stopper of the multi-dose vial has been pierced the vial must be discarded within 28 days.

## 17 PATIENT COUNSELING INFORMATION

- Inform the vaccine recipient or guardian of the potential benefits and risks of immunization with AFLURIA.
- Inform the vaccine recipient or guardian that AFLURIA is an inactivated vaccine that cannot cause influenza but stimulates the immune system to produce antibodies that protect against influenza, and that the full effect of the vaccine is generally achieved approximately 3 weeks after vaccination.
- Instruct the vaccine recipient or guardian to report any severe or unusual adverse reactions to their healthcare provider.
- Provide the vaccine recipient or guardian with Vaccine Information Statements which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).
- Instruct the vaccine recipient or guardian that annual revaccination is recommended.



**Package insert**

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672 Manufactured by:  
673 **Seqirus Pty Ltd.** Parkville, Victoria, 3052, Australia  
674 U.S. License No. 2044  
  
675 Distributed by:  
676 **Seqirus USA Inc.** 25 Deforest Avenue, Summit, NJ 07901, USA 1-855-358-8966  
  
677 AFLURIA is a registered trademark of Seqirus UK Limited or its affiliates.  
678 PharmaJet® and STRATIS® are registered trademarks of PharmaJet, Inc.  
679 Luer-Lok™ is a trademark of Becton, Dickinson and Company Corporation.  
680

# **EXHIBIT 265**

## Title Page and General Information

**BLA number:** 125254

**Related IND numbers:** 12997

**Reviewer Name, Division, and Mail Code:**

Clinical Reviewer: Cynthia Nolletti, MD. CBER/OVRR/DVRPA/Clinical Trials Branch, HFM-485.

Supervisory Reviewer: Joseph Toerner, MD, Team Leader, HFM-475

**Draft Review Completed:** August 29, 2007

**Final Review Completed:** September 19, 2007

**Submission Received by FDA:** March 30, 2007

### 1.2 Product

#### 1.2.1 Established Names:

Influenza virus vaccine

Proprietary or trade names referred to in this BLA and considered equivalent drug product: Afluria, Fluvax, Enzira, Influenza Vaccine-CSL Limited, and CSL Influenza Virus Vaccine (CSL IVV).

#### 1.2.2 Proposed Trade Name: Afluria

#### 1.2.3 Product Formulation:

The 2007-2008 vaccine contains HA from three influenza strains:

- A/Solomon Islands/3/2006 (H1N1) 15µg
- A/Wisconsin/67/2005/ (H3N2) 15µg
- B/Malaysia/2506/2004 15µg

Total 45µg HA antigen

The product is supplied in two presentations:

- Preservative-free pre-filled syringe for single use
- Thimerosal-containing multi-dose vials

Each 5mL vial contains 10 doses.

Each 0.5mL dose contains 50µg thimerosal (24.5 µg mercury)

Afluria contains the following excipients per 0.5mL dose:

- 50 µg of thimerosal (multidose vials only)\*
- 4.1 mg sodium chloride
- 80 µg monobasic sodium phosphate
- 300 µg dibasic sodium phosphate
- 20 µg monobasic potassium phosphate
- 20 µg potassium chloride

- To demonstrate acceptable safety and tolerability of CSL IVV multidose presentation (thimerosal-containing) and CSL IVV pre-filled syringe presentation (thimerosal-free).

#### 8.1.1.1.2 Design Overview:

The study was a Phase III randomized, double-blind, placebo controlled, multicenter trial conducted at nine investigational sites in the United States 12 June 2006 to 25 August 2006. On Visit 1, Vaccine Administration Day 0, informed consent was obtained, and subjects were screened with medical history, physical exam, baseline anti-HI antibody, and pregnancy test. After meeting eligibility criteria, up to 1350 healthy adults  $\geq 18$  to  $\leq 65$  years of age were randomized 1:1:1:1:1 to one of five groups to receive 1 of 3 lots of thimerosal-containing CSL IVV in multidose vial, single lot thimerosal-free CSL IVV in a pre-filled syringe, or single lot placebo (vaccine diluent containing 0.01% w/v thimerosal) in a multidose vial. 0.5mL of study vaccine containing 15  $\mu$ g antigen of each of the three WHO recommended strains of influenza virus for the 2006 Southern Hemisphere or 0.5 mL of placebo were administered intramuscularly in the deltoid muscle.

Post vaccination, subjects were observed for 30 minutes for immediate hypersensitivity or other adverse events (AE's). 5-day Solicited local and systemic AE diary cards and 21-day Unsolicited AE diary cards were issued.

Visit 2, Day 5 (window 5-7): review of 5-day Solicited AE memory aid, All Solicited and Unsolicited AEs/SAEs recorded, medication review.

Visit 3, Day 21 (window 21-24), Exit Evaluation: anti-HI antibody titers, review of 21-day Unsolicited AE diary card, assessment of any SAE's, medication review, targeted physical exam.

**Table 8.1.1-1 Study Procedures and Assessments CSLCT-FLU-05-09**

Study Visit	Screen* 0	1	2	3	Early Termination
Study Day	-28 to -1	0	5- 7	21- 24	
<b>Procedure</b>					
Obtain Informed Consent	X				
Review Eligibility Criteria	X	X			
Review Influenza Illness and Vaccination History	X	X			
Review Health Status				X	X
Oral Temperature, Blood Pressure and Heart Rate	X	X			
Medical History	X	X			
Targeted Physical Examination, as indicated	X	X		X	X
Urine or Serum Pregnancy Test	X <sup>†</sup>	X <sup>†</sup>			
Concomitant Medications	X	X	X	X	X
Blood for Antibody Assays		X <sup>†</sup>		X	X
Randomization		X			

SAP for the trial. (This is explained in Module 2 Volume 1 Section 2.5 Clinical Overview, p25 of 58.)

#### 8.1.1.2 **Results, study CSLCT-FLU-05-09**

##### 8.1.1.2.1 **Populations enrolled and analyzed**

○ A total of 1359 subjects were randomized, 1357 received either CSL IVV multidose presentation (n = 823), CSL IVV pre-filled syringe (n=266), or thimerosal multidose Placebo (n=268). The first subject enrolled on June 12, 2006, and the last visit for the last subject enrolled was on August 25, 2006. The safety population included all subjects who received CSL IVV (n=1357)

○ 1350 subjects (99.5%) completed the study. Of the nine subjects who did not complete the study, 5 were lost to follow-up, 1 withdrew consent, and 2 were randomized but not vaccinated, and one was withdrawn because their data could not be source verified. No subject was withdrawn due to an AE.

##### **Protocol Deviations**

○ A total of 1357 out of 1359 subjects received the study vaccine and were included in the safety population.

○ A total of 1341 subjects were included in the Evaluable Population and 1241 subjects were included in the Per Protocol Population.

○ According to the applicant, of the 1357 subjects who received Study Vaccine:  
12 did not provide both a pre and a post-vaccination blood sample  
5 subjects received prohibited oral prednisone. One of these (27FBA106) also lacked pre and post vaccination blood samples for immunogenicity assessments above)  
Total non-evaluable population:  $12 + 4 = 16$   
Evaluable population:  $1357 - 16 = 1341$

101 subjects received an incorrectly stored vaccine  
1 subject was incorrectly randomized  
Total non-per protocol population:  $12+4+101+1=118$ .  
Per Protocol population:  $1357 - 118 = 1239$ .

The applicant's medical monitor reviewed subjects that received contra-indicated medications post-vaccination and prior to collection of post-vaccination serology. Those subjects whose violations were deemed likely to impact on immunogenicity assessments, eg, use of oral steroids, were excluded from the  
Evaluable population for efficacy analysis prior to unblinding

The following table is based on the applicant's Table 2 Module 5 Volume 1 Section 5.3.1-1, p53. These numbers were confirmed by review of the electronic datasets.



Adverse Event	CSL IVV Multi-dose n=823 %	CSL IVV Single use n=266 %	Placebo thimerosal n=266 %	CSL IVV n=206 %	Influsplit No thimerosal n=69 %
Age group (years)	≥18 to <65	≥18 to <65	≥18 to <65	≥65	≥65
Swelling	10.0	6.8	0.7	11.2	0
Redness	17.7	12.0	8.2	23.3	8.7
Pain	37.4	47.0	9.3	8.7	0
Tenderness	57.1	68.0	17.9	33.5	17.4
Bruising	5.1	3.8	1.1	4.4	1.4
Fever ≥37.7°C (99.86°F)	1.1	1.5	0.7	1.0	1.4
Headache	25.2	27.1	25.7	14.6	10.1
Malaise	18.8	21.4	18.7	9.7	7.2
Myalgia	12.2	15.0	9.0	14.1	10.1
Chills/ Shivering	3.3	2.3	2.2	6.8	5.8
Nausea	5.7	8.6	8.6	3.4	2.9
Vomiting	0.9	0.8	0.7	0	0

CSL IVV=Afluria or CSL IVV, CSL's trivalent inactivated influenza vaccine

Reviewer comment: There appeared to be a greater proportion of subjects who experienced injection site pain and tenderness, headache and malaise among CSL IVV recipients than in the Influsplit group, and among younger subjects as compared with older adults. The majority of these events were mild or moderate, with few severe in intensity.

These reactions are considered to be related or caused by the study vaccine.

**Table 10-7 Proportion of Subjects with Solicited AEs within 4 days post-vaccination. Post hoc integrated analyses of CSLCT-NHF-05-11, CSLCT-NHF-05-13, CSLCT-NHF-04-99 stratified by age <65 and ≥65 years**

	Integrated totals: CSLCT-NHF-05-11, CSLCT-NHF-05-13, and CSLCT-NHF-04-99			
	≥18 to <65 years			≥65 years
Adverse Event	CSL IVV n=309 %	Mutagrip n=140 %	CSL IVV n=137 %	Mutagrip n=60 %

# **EXHIBIT 266**



## Package insert

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFLURIA® QUADRIVALENT safely and effectively. See full prescribing information for AFLURIA QUADRIVALENT.

#### AFLURIA QUADRIVALENT, Influenza Vaccine

##### Suspension for Intramuscular Injection

##### 2019-2020 Formula

##### Initial U.S. Approval (AFLURIA QUADRIVALENT): 2016

### RECENT MAJOR CHANGES

Indications and Usage (1)	10/2018
Dosage and Administration (2)	10/2018

### INDICATIONS AND USAGE

- AFLURIA QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. (1)
- AFLURIA QUADRIVALENT is approved for use in persons 6 months of age and older. (1)

### DOSAGE AND ADMINISTRATION

For intramuscular injection only, by needle and syringe (6 months and older) or by PharmaJet®Stratis® Needle-Free Injection System (18 through 64 years). (2)

Age	Dose	Schedule
6 months through 35 months	One or two doses <sup>a</sup> , 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses <sup>a</sup> , 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5 mL	Not Applicable

<sup>a</sup>1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines. (2)

### DOSAGE FORMS AND STRENGTHS

AFLURIA QUADRIVALENT is a suspension for injection supplied in three presentations:

- 0.25 mL pre-filled syringe (single dose) (3, 11)
- 0.5 mL pre-filled syringe (single dose) (3, 11)
- 5 mL multi-dose vial (ten doses) (3, 11)

### CONTRAINDICATIONS

- Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine. (4, 11)

### WARNINGS AND PRECAUTIONS

- If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA QUADRIVALENT should be based on careful consideration of the potential benefits and risks. (5.1)
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. (5.2)

### ADVERSE REACTIONS

AFLURIA QUADRIVALENT administered by needle and syringe:

- In adults 18 through 64 years, the most commonly reported injection-site adverse reaction was pain (≥ 40%). The most common systemic adverse events were myalgia and headache (≥ 20%). (6.1)
- In adults 65 years of age and older, the most commonly reported injection-site adverse reaction was pain (≥ 20%). The most common systemic adverse event was myalgia (≥ 10%). (6.1)
- In children 5 through 8 years, the most commonly reported injection-site adverse reactions were pain (≥ 50%), redness and swelling (≥ 10%). The most common systemic adverse event was headache (≥ 10%). (6.1)
- In children 9 through 17 years, the most commonly reported injection-site adverse reactions were pain (≥ 50%), redness and swelling (≥ 10%). The most common systemic adverse events were headache, myalgia, and malaise and fatigue (≥ 10%). (6.1)
- In children 6 months through 35 months of age, the most commonly reported injection-site reactions were pain and redness (≥ 20%). The most common systemic adverse events were irritability (≥ 30%), diarrhea and loss of appetite (≥ 20%). (6.1)
- In children 36 through 59 months of age, the most commonly reported injection site reactions were pain (≥ 30%) and redness (≥ 20%). The most commonly reported systemic adverse events were malaise and fatigue, and diarrhea (≥ 10%). (6.1)

AFLURIA (trivalent formulation) administered by the PharmaJet Stratis Needle-Free Injection System:

- In adults 18 through 64 years of age, the most commonly reported injection-site adverse reactions were tenderness (≥ 80%), swelling, pain, redness (≥ 60%), itching (≥ 20%) and bruising (≥ 10%). The most common systemic adverse events were myalgia, malaise (≥ 30%), and headache (≥ 20%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Seqirus USA Inc. at 1-855-358-8966 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

### USE IN SPECIFIC POPULATIONS

- The safety and effectiveness of AFLURIA QUADRIVALENT in persons less than 6 months of age have not been established. (8.4)
- Antibody responses were lower in geriatric subjects than in younger adults. (8.5)
- Pregnancy: There is a pregnancy exposure registry that monitors outcomes in women exposed to AFLURIA QUADRIVALENT during pregnancy. Enroll in the pregnancy registry by calling 1-855-358-8966 or sending an email to [us.medicalinformation@seqirus.com](mailto:us.medicalinformation@seqirus.com). (8.1).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2019

**Package insert**

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- 3 DOSAGE FORMS AND STRENGTHS**
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**Package insert****FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE**

AFLURIA® QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

AFLURIA QUADRIVALENT is approved for use in persons 6 months of age and older.

**2 DOSAGE AND ADMINISTRATION****For intramuscular (IM) use only.**

- By needle and syringe (6 months of age and older)
- By PharmaJet® Stratis® Needle-Free Injection System (18 through 64 years of age)

The dose and schedule for AFLURIA QUADRIVALENT are presented in Table 1.

**Table 1: AFLURIA QUADRIVALENT Dosage and Schedule**

Age	Dose	Schedule
6 months through 35 months	One or two doses <sup>a</sup> , 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses <sup>a</sup> , 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5mL	Not Applicable

<sup>a</sup>1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

Immediately before use, shake thoroughly and inspect visually. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever suspension and container permit. If either of these conditions exists, the vaccine should not be administered.

When using the single-dose pre-filled syringe, shake the syringe thoroughly and administer the dose immediately.

When using the multi-dose vial, shake the vial thoroughly before withdrawing each dose, and administer the dose immediately. No more than 10 doses (0.25 mL or 0.5 mL) should be withdrawn from the multi-dose vial.

- Needle and Syringe: Draw up the exact dose using a separate sterile needle and syringe for each individual patient. It is recommended that small syringes (0.5 mL or 1 mL) be used to minimize any product loss.
- PharmaJet Stratis Needle-Free Injection System: For instructions on withdrawal of a 0.5 mL dose and use of the PharmaJet Stratis Needle-Free Injection System, refer to the Instructions For Use for the PharmaJet Stratis Needle-Free Injection System.



## Package insert

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The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle of the upper arm if muscle mass is adequate) in persons 12 months through 35 months of age, or the deltoid muscle of the upper arm in persons  $\geq 36$  months of age.

### 3 DOSAGE FORMS AND STRENGTHS

AFLURIA QUADRIVALENT is a sterile suspension for intramuscular injection (*see Description [11]*).

AFLURIA QUADRIVALENT is supplied in three presentations:

- 0.25 mL pre-filled syringe (single dose, for persons 6 months through 35 months of age)
- 0.5 mL pre-filled syringe (single dose, for persons 36 months of age and older).
- 5 mL multi-dose vial ( for persons 6 months of age and older).

### 4 CONTRAINDICATIONS

AFLURIA QUADRIVALENT is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine (*see Description [11]*).

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Guillain-Barré Syndrome

If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA QUADRIVALENT should be based on careful consideration of the potential benefits and risks.

The 1976 swine influenza vaccine was associated with an increased frequency of GBS. Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than one additional case per 1 million persons vaccinated.

#### 5.2 Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

#### 5.3 Altered Immunocompetence

If AFLURIA QUADRIVALENT is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

#### 5.4 Limitations of Vaccine Effectiveness

Vaccination with AFLURIA QUADRIVALENT may not protect all individuals.



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### 6 ADVERSE REACTIONS

In adults 18 through 64 years of age, the most commonly reported injection-site adverse reaction observed in clinical studies with AFLURIA QUADRIVALENT administered by needle and syringe was pain ( $\geq 40\%$ ). The most common systemic adverse events observed were myalgia and headache ( $\geq 20\%$ ).

In adults 65 years of age and older, the most commonly reported injection-site adverse reaction observed in clinical studies with AFLURIA QUADRIVALENT administered by needle and syringe was pain ( $\geq 20\%$ ). The most common systemic adverse event observed was myalgia ( $\geq 10\%$ ).

The safety experience with AFLURIA (trivalent formulation) is relevant to AFLURIA QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions (see [Description \[11\]](#)).

In adults 18 through 64 years of age, the most commonly reported injection-site adverse reactions observed in a clinical study with AFLURIA (trivalent formulation) using the PharmaJet Stratis Needle-Free Injection System were tenderness ( $\geq 80\%$ ), swelling, pain, redness ( $\geq 60\%$ ), itching ( $\geq 20\%$ ) and bruising ( $\geq 10\%$ ). The most common systemic adverse events were myalgia, malaise ( $\geq 30\%$ ) and headache ( $\geq 20\%$ ).

In children 5 through 8 years, the most commonly reported injection-site adverse reactions when AFLURIA QUADRIVALENT was administered by needle and syringe were pain ( $\geq 50\%$ ) and redness and swelling ( $\geq 10\%$ ). The most common systemic adverse event was headache ( $\geq 10\%$ ).

In children 9 through 17 years, the most commonly reported injection-site adverse reactions when AFLURIA QUADRIVALENT was administered by needle and syringe were pain ( $\geq 50\%$ ) and redness and swelling ( $\geq 10\%$ ). The most common systemic adverse events were headache, myalgia, and malaise and fatigue ( $\geq 10\%$ ).

In children 6 months through 35 months of age, the most frequently reported injection site reactions in the clinical study with AFLURIA QUADRIVALENT administered by needle and syringe were pain and redness ( $\geq 20\%$ ). The most common systemic adverse events were irritability ( $\geq 30\%$ ), diarrhea and loss of appetite ( $\geq 20\%$ ).

In children 36 through 59 months of age, the most commonly reported injection site reactions were pain ( $\geq 30\%$ ) and redness ( $\geq 20\%$ ). The most commonly reported systemic adverse events were malaise and fatigue, and diarrhea ( $\geq 10\%$ ).

#### 6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a vaccine cannot be directly compared to rates in the clinical studies of another vaccine and may not reflect the rates observed in clinical practice.





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### *Adults*

Clinical safety data for AFLURIA QUADRIVALENT in adults have been collected in one clinical trial, Study 1, a randomized, double-blind, active-controlled trial conducted in the U.S. in 3449 subjects ages 18 years and older. Subjects in the safety population received one dose of either AFLURIA QUADRIVALENT (N=1721) or one of two formulations of comparator trivalent influenza vaccine (AFLURIA, TIV-1 N=864 or TIV-2 N=864) each containing an influenza type B virus that corresponded to one of the two B viruses in AFLURIA QUADRIVALENT (a type B virus of the Yamagata lineage or a type B virus of the Victoria lineage), respectively. The mean age of the population was 58 years, 57% were female, and racial groups consisted of 82% White, 16% Black, and 2% other; 5% of subjects were Hispanic/Latino. The age sub-groups were 18 through 64 years and 65 years and older with mean ages of 43 years and 73 years, respectively. In this study, AFLURIA QUADRIVALENT and comparator trivalent influenza vaccines were administered by needle and syringe (*see Clinical Studies [14]*).

Local (injection-site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination (Table 2). Injection site cellulitis, cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and swelling/lump), and Grade 3 swelling/lump were monitored for 28 days post-vaccination. Unsolicited adverse events were collected for 28 days post-vaccination. Serious adverse events (SAEs), including deaths, were collected for 180 days post-vaccination.



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**Table 2: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA QUADRIVALENT or Trivalent Influenza Vaccine (Study 1)<sup>a</sup>**

	Percentage (%) <sup>b</sup> of Subjects in each Age Cohort Reporting an Event											
	Subjects 18 through 64 years						Subjects ≥ 65 years					
	AFLURIA Quadrivalent N= 854 <sup>c</sup>		TIV-1 N= 428 <sup>c</sup>		TIV-2 N= 430 <sup>c</sup>		AFLURIA Quadrivalent N= 867 <sup>c</sup>		TIV-1 N= 436 <sup>c</sup>		TIV-2 N= 434 <sup>c</sup>	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
<b>Local Adverse Reactions <sup>d</sup></b>												
Pain	47.9	0.7	43.7	1.4	50.7	1.2	24.6	0.1	22.7	0	21.0	0.2
Swelling/Lump	3.7	0.1	2.3	0	3.5	0.2	3.2	0.5	1.8	0	1.6	0
Redness	2.9	0	2.8	0	2.8	0	4.2	0.3	2.1	0	2.5	0.2
<b>Systemic Adverse Events <sup>e</sup></b>												
Myalgia (muscle ache)	25.5	1.9	23.4	1.4	24.2	1.2	12.7	0.3	14.0	0.7	12.2	0.5
Headache	21.7	1.7	15.2	0.9	19.1	1.2	8.4	0	7.1	0.2	7.8	0.7
Malaise	8.9	0.7	9.1	0	9.3	0.7	4.4	0.5	5.0	0.2	5.1	0.2
Nausea	6.9	0.6	7.7	0.5	6.3	1.2	1.6	0	1.8	0	2.1	0.2
Chills	4.8	0.6	4.4	0.2	4.7	0.5	2.0	0	2.1	0.5	1.4	0.2
Vomiting	1.5	0.4	0.9	0	2.3	0.7	0.5	0.1	0	0	0.7	0.2
Fever	1.1	0.4	0.9	0	0.5	0	0.2	0	0.9	0	0.5	0.2

Abbreviations: Gr 3, Grade 3.

<sup>a</sup> NCT02214225

<sup>b</sup> Proportion of subjects reporting each solicited local adverse reaction or systemic adverse event by study vaccine group based on the number of subjects contributing any follow up safety information for at least one data value of an individual sign/symptom.

<sup>c</sup> N = number of subjects in the Safety Population for each study vaccine group.

<sup>d</sup> Local adverse reactions: Grade 3 pain is that which prevents daily activity; Swelling/Lump and redness: any = ≥ 20mm diameter, Grade 3 = ≥ 100mm diameter.

<sup>e</sup> Systemic adverse events: Fever: any = ≥ 100.4°F (Oral), Grade 3 = ≥ 102.2°F (Oral); Grade 3 for all other adverse events is that which prevents daily activity.

In the 28 days following vaccination, no subject experienced cellulitis or a cellulitis-like reaction. All Grade 3 swelling/lump reactions began within 7 days of vaccination and are included in Table 2.

In the 28 days following vaccination, 20.5%, 20.1%, and 20.7% of adults 18 through 64 years and 20.3%, 24.1%, and 20.0% of adults ≥ 65 years who received AFLURIA QUADRIVALENT, TIV-1, and TIV-2, respectively, reported unsolicited adverse events. Rates of individual events were similar between treatment groups, and most events were mild to moderate in severity.

In the 180 days following vaccination, 2.3%, 1.6%, and 1.5% of all subjects who received AFLURIA QUADRIVALENT, TIV-1, and TIV-2, respectively, experienced SAEs, including

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143 six deaths, five in the AFLURIA QUADRIVALENT group and one in the TIV-2 group. The  
144 majority of SAEs occurred after Study Day 28 and in subjects  $\geq 65$  years of age who had co-  
145 morbid illnesses. No SAEs or deaths appeared related to the study vaccines.

146 Safety information has also been collected in a clinical study of AFLURIA (trivalent  
147 formulation) administered using the PharmaJet Stratis Needle-Free Injection System (Study 2).  
148 Study 2 included 1,247 subjects for safety analysis, ages 18 through 64 years, randomized to  
149 receive AFLURIA by either the PharmaJet Stratis Needle-Free Injection System (624 subjects)  
150 or needle and syringe (623 subjects). No deaths or vaccine-related serious adverse events were  
151 reported in Study 2. Local (injection-site) adverse reactions and systemic adverse events were  
152 solicited for 7 days post-vaccination (Table 3).



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**Table 3: Proportion of Subjects 18 through 64 Years of Age with Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA (trivalent formulation) by PharmaJet Stratis Needle-Free Injection System or Needle and Syringe (Study 2)<sup>a</sup>**

	Percentage <sup>b</sup> of Subjects Reporting Event			
	Subjects 18 through 64 years			
	AFLURIA (trivalent formulation)			
	PharmaJet Stratis Needle-Free Injection System N=540-616 <sup>c</sup>		Needle and Syringe N=599-606 <sup>c</sup>	
	Any	Grade 3	Any	Grade 3
<b>Local Adverse Reactions <sup>d</sup></b>				
Tenderness	89.4	2.1	77.9	1.0
Swelling	64.8	1.7	19.7	0.2
Pain	64.4	0.8	49.3	0.7
Redness	60.1	1.3	19.2	0.3
Itching <sup>f</sup>	28.0	0.0	9.5	0.2
Bruising	17.6	0.2	5.3	0.0
<b>Systemic Adverse Events <sup>e</sup></b>				
Myalgia	36.4	0.8	35.5	1.0
Malaise	31.2	0.7	28.4	0.5
Headache	24.7	1.3	22.1	1.3
Chills	7.0	0.2	7.2	0.2
Nausea	6.6	0.2	6.5	0.0
Vomiting	1.3	0.0	1.8	0.2
Fever	0.3	0.0	0.3	0.0

<sup>a</sup> NCT01688921

<sup>b</sup> Proportion of subjects reporting each local adverse reaction or systemic adverse event by treatment group based on the number of subjects contributing at least one data value for an individual sign/symptom (individual event denominators).

<sup>c</sup> N = number of subjects in the Safety Population for each treatment group. Denominators for the PharmaJet Stratis Needle-Free Injection System group were: N=540 for itching and N=605-616 for all other parameters. Denominators for the needle and syringe group were: N=527 for itching and N=599-606 for all other parameters.

<sup>d</sup> Local adverse reactions: Grade 3 is pain, tenderness or itching that prevents daily activity; Swelling, redness or bruising: any =  $\geq 25$ mm diameter, Grade 3 =  $\geq 100$ mm diameter.

<sup>e</sup> Systemic adverse events: Fever: any =  $\geq 100.4^{\circ}\text{F}$  (Oral), Grade 3 =  $\geq 102.2^{\circ}\text{F}$  (Oral); Grade 3 for all other adverse events is that which prevents daily activity.

<sup>f</sup> A total of 155 subjects (approximately randomly distributed between PharmaJet Stratis Needle-Free Injection System and needle and syringe groups) received Diary Cards without itching listed as a solicited symptom.

In adults 18 through 64 years who received AFLURIA (trivalent formulation) administered by PharmaJet Stratis Needle-Free Injection System, commonly reported unsolicited adverse events were headache (4.2%), injection site hematoma (1.8%), injection site erythema (1.1%), myalgia (1.0%) and nausea (1.0%).



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#### ***Children 5 Years Through 17 Years of Age***

Clinical safety data for AFLURIA QUADRIVALENT in older children and adolescents have been collected in one clinical trial, Study 3, a randomized, observer-blinded, comparator-controlled trial conducted in the U.S. in 2278 subjects aged 5 through 17 years. Subjects were stratified into one of two age cohorts of 5 through 8 years or 9 through 17 years (51.2% and 48.8% of the study population, respectively). The mean age of the population was 9.5 years, 52.1% were male, and racial groups consisted of 73.3% White, 20.7% Black, 0.8% Asian, 0.3% American Indian/Native American, and 0.7% Native Hawaiian/Pacific Islander; 23.8% of subjects were Hispanic/Latino. The mean ages of subjects 5 through 8 years and 9 through 17 years were 6.7 years and 12.5 years, respectively. Subjects in the safety population (N=2252) received either AFLURIA QUADRIVALENT (N=1692) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=560). Study subjects were scheduled to receive either a single vaccination or two vaccinations 28 days apart based on their previous vaccination history. In this study, AFLURIA QUADRIVALENT and comparator vaccine were administered by needle and syringe (see *Clinical Studies [14]*).

Local (injection site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination. Cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and swelling/lump) at the injection site were monitored for 28 days post-vaccination. Subjects were instructed to report and return to clinic within 24 hours in the event of a cellulitis-like reaction. Unsolicited adverse events were collected for 28 days post-vaccination. All solicited local adverse reactions and systemic adverse events following any vaccination (first or second dose) are presented in Table 4.



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**Table 4: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA QUADRIVALENT or Comparator (Study 3)<sup>a</sup>**

	Percentage (%) <sup>b</sup> of Subjects in each Age Cohort Reporting an Event							
	Subjects 5 through 8 years				Subjects 9 through 17 years			
	AFLURIA Quadrivalent N= 828-829 <sup>c</sup>		Comparator N= 273-274 <sup>c</sup>		AFLURIA Quadrivalent N= 790-792 <sup>c</sup>		Comparator N= 261 <sup>c</sup>	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
<b>Local Adverse Reactions <sup>d</sup></b>								
Pain	51.3	0.8	49.6	0.7	51.5	0.3	45.2	0.4
Redness	19.4	3.5	18.6	1.8	14.8	1.9	16.1	1.9
Swelling/Lump	15.3	3.4	12.4	2.2	12.2	2.0	10.7	1.9
<b>Systemic Adverse Events <sup>e</sup></b>								
Headache	12.3	0.1	10.6	0.4	18.8	0.4	14.6	0.4
Myalgia	9.8	0.1	11.3	0.4	16.7	0.3	11.1	0.4
Malaise and Fatigue	8.8	0.4	5.8	0	10.0	0.4	7.7	0
Nausea	7.1	0.1	8.4	0	7.7	0	8.0	0
Diarrhea	5.2	0	3.6	0	5.4	0	4.2	0
Fever	4.5	1.2	3.6	0.7	2.1	0.5	0.8	0
Vomiting	2.4	0.2	4.4	0	1.8	0	2.3	0

Abbreviations: Gr 3, Grade 3 (severe); Comparator, Comparator quadrivalent influenza vaccine [Fluarix® Quadrivalent (GlaxoSmithKline Biologicals)]

<sup>a</sup> NCT02545543

<sup>b</sup> Percent (%) is derived from the number of subjects that reported the event divided by the number of subjects in the Solicited Safety Population with non-missing data for each age cohort, treatment group, and each solicited parameter.

<sup>c</sup> N = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety data) for each study vaccine group.

<sup>d</sup> Local adverse reactions: Grade 3 pain is that which prevents daily activity; swelling/lump and redness: any = > 0mm diameter, Grade 3 = > 30mm diameter.

<sup>e</sup> Systemic adverse events: Fever: any = ≥ 100.4°F (Oral), Grade 3 = ≥ 102.2°F (Oral); Grade 3 for all other adverse events is that which prevents daily activity or requires significant medical intervention.

In subjects 5 through 8 years of age, all solicited local adverse reactions and systemic adverse events were reported at lower frequencies after the second vaccination than after the first vaccination with AFLURIA QUADRIVALENT with the exception of vomiting (which occurred at the same rate of 2.2% after each vaccination).

One subject, 8 years of age, experienced a cellulitis-like reaction at the injection site after vaccination with AFLURIA QUADRIVALENT.

The most commonly reported unsolicited adverse events in the 28 days following the first or second dose of AFLURIA QUADRIVALENT in subjects 5 through 8 years of age were cough (2.4%), pyrexia (1.8%), rhinorrhea (1.2%), and headache (1.0%), and were similar to the comparator.



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For subjects ages 9 through 17 years who received AFLURIA QUADRIVALENT, the most commonly reported unsolicited adverse events in the 28 days following vaccination were oropharyngeal pain (1.6%), cough (1.3%), and upper respiratory tract infection (1.0%), and were similar to the comparator.

No deaths were reported in Study 3. In the 180 days following vaccinations, AFLURIA QUADRIVALENT and comparator vaccine recipients experienced similar rates of serious adverse events (SAEs). None of the SAEs appeared related to the study vaccines except for one case of influenza B infection (considered a vaccine failure) in an AFLURIA QUADRIVALENT recipient.

***Children 6 Months Through 59 Months of Age***

Clinical safety data for AFLURIA QUADRIVALENT in infants and young children have been collected in one clinical trial, Study 4, a randomized, observer-blind, comparator-controlled trial conducted in the U.S. in 2247 subjects aged 6 through 59 months. Subjects were stratified into one of two age cohorts of 6 through 35 months or 36 through 59 months (41.6% and 58.4% of the study population, respectively). The mean age of the population was 36.6 months, 51.6% were male, and racial groups consisted of 71.0% White, 21.5% Black, 1.1% Asian, 0.7% Native Hawaiian/Pacific Islander, and 0.3% American Indian/Native American; 26.4% of subjects were Hispanic/Latino. The mean ages of subjects 6 through 35 months and 36 through 59 months were 21.7 months and 47.1 months, respectively. Subjects in the safety population (N=2232) received either AFLURIA QUADRIVALENT (N=1673) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=559). Study subjects were scheduled to receive either a single vaccination or two vaccinations 28 days apart based on their previous vaccination history. In this study, AFLURIA QUADRIVALENT and comparator vaccine were administered by needle and syringe (see *Clinical Studies [14]*).

Local (injection site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination. Cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and swelling/lump) at the injection site were monitored for 28 days post-vaccination. Subjects were instructed to report and return to clinic within 24 hours in the event of a cellulitis-like reaction. Unsolicited adverse events were collected for 28 days post-vaccination, and SAEs for 6 months following the last vaccination. All solicited local adverse reactions and systemic adverse events following any vaccination (first or second dose) are presented in Table 5.





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**Table 5: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA QUADRIVALENT or Comparator QIV (Study 4)<sup>a</sup>**

	Percentage (%) <sup>b</sup> of Subjects in each Age Cohort Reporting an Event							
	6 through 35 months				36 through 59 months			
	AFLURIA Quadrivalent N= 668-669 <sup>c</sup>		Comparator N= 226-227 <sup>c</sup>		AFLURIA Quadrivalent N= 947-949 <sup>c</sup>		Comparator N= 317-318 <sup>c</sup>	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
<b>Local Adverse Reactions<sup>d</sup></b>								
Pain	20.8	0.1	25.6	0.4	35.5	0	31.4	0.6
Redness	20.8	0.6	17.6	1.8	22.4	2.3	20.8	5.3
Swelling/Lump	6.1	0.4	6.2	0.9	10.1	1.7	12.9	2.5
<b>Systemic Adverse Events<sup>e</sup></b>								
Irritability	32.9	0.7	28.2	0.4	-	-	-	-
Diarrhea	24.2	0.1	25.6	0.4	12.1	0.1	8.8	0.6
Loss of Appetite	20.0	0.3	19.4	0.4	-	-	-	-
Malaise and Fatigue	-	-	-	-	14.3	0.5	13.2	0.3
Myalgia	-	-	-	-	9.9	0.1	9.4	0
Nausea and/or vomiting	9.4	0.7	11.0	0	9.2	0.4	6.6	0.3
Headache	-	-	-	-	6.2	0.4	5.0	0
Fever <sup>f</sup>	7.2	2.5	11.9	2.6	4.8	1.2	6.0	0.9

Abbreviations: Gr 3, Grade 3 (severe); Comparator, Comparator quadrivalent influenza vaccine [Fluzone® Quadrivalent (Sanofi Pasteur)]

<sup>a</sup> NCT02914275

<sup>b</sup> Percent (%) is derived from the number of subjects that reported the event divided by the number of subjects in the Solicited Safety Population with non-missing data for each age cohort, treatment group, and each solicited parameter.

<sup>c</sup> N = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety data) for each study vaccine group.

<sup>d</sup> Local adverse reactions: Grade 3 pain is that which prevents daily activity (36 through 59 month subjects); or cried when limb was moved or spontaneously painful (6 through 35 month subjects); Swelling/Lump and redness: any = ≥ 0mm diameter, Grade 3 = ≥ 30mm diameter.

<sup>e</sup> Systemic adverse events: Fever: any = ≥ 99.5°F (Axillary), Grade 3 = ≥ 101.3°F (Axillary); Grade 3 for all other adverse events is that which prevents daily activity; Irritability, Loss of Appetite, Malaise and Fatigue, Myalgia and Headache are age specific systemic adverse events, where “-” denotes event was not applicable to that age cohort.

<sup>f</sup> Prophylactic antipyretics (acetaminophen or ibuprofen-containing medications) were not permitted. Antipyretics used to treat fever were permitted and rates of use were as follows: 6 through 35 months (Afluria QIV 5.9%, Comparator QIV 9.0%); 36 through 59 months (Afluria QIV 3.7%, Comparator QIV 2.5%).

In subjects 6 through 35 months of age, all solicited local adverse reactions and systemic adverse events were reported at lower frequencies after the second vaccination than after the first vaccination with AFLURIA QUADRIVALENT.

In subjects 36 through 59 months of age, all solicited local adverse reactions and systemic adverse events were reported at lower frequencies after the second vaccination than after the first vaccination with AFLURIA QUADRIVALENT.

The most commonly reported unsolicited adverse events in the 28 days following the first or second dose of AFLURIA QUADRIVALENT in subjects 6 through 35 months of age were rhinorrhea (11.2%), cough (10.4%), pyrexia (6.3%), upper respiratory tract infection (4.8%),



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diarrhea (3.7%), otitis media (2.4%), vomiting (2.4%), nasal congestion (2.4%), nasopharyngitis (1.9%), irritability (1.7%), ear infection (1.6%), croup infectious (1.4%), teething (1.3%), rash (1.2%), influenza like illness (1.0%) and fatigue (1.0%), and were similar to comparator.

The most commonly reported unsolicited adverse events in the 28 days following the first or second dose of AFLURIA QUADRIVALENT in subjects 36 through 59 months of age were cough (7.7%), rhinorrhea (4.9%), pyrexia (3.7%), upper respiratory tract infection (2.5%), vomiting (2.1%), nasal congestion (1.6%), nasopharyngitis (1.7%), oropharyngeal pain (1.2%) diarrhea (1.1%) and fatigue (1.1%), and were similar to the comparator.

No deaths were reported in Study 4. In the 180 days following vaccinations, AFLURIA QUADRIVALENT and comparator vaccine recipients experienced similar rates of serious adverse events (SAEs), none of which were related to study vaccines. No vaccine-related febrile seizures occurred in Study 4. Unrelated SAEs of febrile seizures occurred in two AFLURIA QUADRIVALENT recipients (6 through 35 months age group) at 43 and 104 days post-vaccinations.

## 6.2 Postmarketing Experience

Because postmarketing reporting of adverse events is voluntary and from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The adverse events described have been included in this section because they: 1) represent reactions that are known to occur following immunizations generally or influenza immunizations specifically; 2) are potentially serious; or 3) have been reported frequently. There are limited postmarketing data available for AFLURIA QUADRIVALENT. The adverse events listed below reflect experience in both children and adults and include those identified during post-approval use of AFLURIA (trivalent formulation) outside the U.S. since 1985.

The post-marketing experience with AFLURIA (trivalent formulation) included the following:

### **Blood and lymphatic system disorders**

Thrombocytopenia

### **Immune system disorders**

Allergic or immediate hypersensitivity reactions including anaphylactic shock and serum sickness

### **Nervous system disorders**

Neuralgia, paresthesia, convulsions (including febrile seizures), encephalomyelitis, encephalopathy, neuritis or neuropathy, transverse myelitis, and GBS

### **Vascular disorders**

Vasculitis which may be associated with transient renal involvement

### **Skin and subcutaneous tissue disorders**



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Pruritus, urticaria, and rash

### General disorders and administration site conditions

Cellulitis and large injection site swelling

Influenza-like illness

## 7 DRUG INTERACTIONS

No interaction studies have been performed on interaction between influenza vaccines in general and other vaccines or medications.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AFLURIA QUADRIVALENT during pregnancy. Women who are vaccinated with AFLURIA QUADRIVALENT during pregnancy are encouraged to enroll in the registry by calling 1-855-358-8966 or sending an email to Seqirus at [us.medicalinformation@seqirus.com](mailto:us.medicalinformation@seqirus.com).

#### Risk summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Data for AFLURIA (trivalent formulation) administered to pregnant women are relevant to AFLURIA QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions (see [Description \[11\]](#)). There are limited data for AFLURIA QUADRIVALENT administered to pregnant women, and available data for AFLURIA (trivalent formulation) administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

There were no developmental toxicity studies of AFLURIA QUADRIVALENT performed in animals. A developmental toxicity study of AFLURIA (trivalent formulation) has been performed in female rats administered a single human dose [0.5 mL (divided)] of AFLURIA (trivalent formulation) prior to mating and during gestation. This study revealed no evidence of harm to the fetus due to AFLURIA (trivalent formulation) (see [8.1 Data](#)).

#### Clinical Considerations

##### *Disease-associated Maternal and/or Embryo-Fetal Risk*

Pregnant women are at increased risk for severe illness due to influenza compared to non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

#### Data

##### *Animal Data*



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In a developmental toxicity study, female rats were administered a single human dose [0.5 mL (divided)] of AFLURIA (trivalent formulation) by intramuscular injection 21 days and 7 days prior to mating, and on gestation day 6. Some rats were administered an additional dose on gestation day 20. No vaccine-related fetal malformations or variations and no adverse effects on pre-weaning development were observed in the study.

## 8.2 Lactation

### Risk Summary

It is not known whether AFLURIA QUADRIVALENT is excreted in human milk. Data are not available to assess the effects of AFLURIA QUADRIVALENT on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AFLURIA QUADRIVALENT and any potential adverse effects on the breastfed child from AFLURIA QUADRIVALENT or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

## 8.4 Pediatric Use

The safety and effectiveness of AFLURIA QUADRIVALENT in persons less than 6 months of age have not been established.

The PharmaJet Stratis Needle-Free Injection System is not approved as a method of administering AFLURIA QUADRIVALENT to children and adolescents less than 18 years of age due to lack of adequate data supporting safety and effectiveness in this population.

## 8.5 Geriatric Use

In clinical studies, AFLURIA QUADRIVALENT has been administered to, and safety information collected for, 867 subjects aged 65 years and older (*see Adverse Reactions [6]*). The 65 years and older age group included 539 subjects 65 through 74 years and 328 subjects 75 years and older. After administration of AFLURIA QUADRIVALENT, hemagglutination-inhibiting antibody responses were non-inferior to comparator trivalent influenza (TIV-1 and TIV-2) in persons 65 years of age and older, but were lower than younger adult subjects (*see Clinical Studies [14]*).

The PharmaJet Stratis Needle-Free Injection System is not approved as a method of administering AFLURIA QUADRIVALENT to adults 65 years of age and older due to lack of adequate data supporting safety and effectiveness in this population.

## 11 DESCRIPTION

AFLURIA QUADRIVALENT, Influenza Vaccine for intramuscular injection, is a sterile, clear, colorless to slightly opalescent suspension with some sediment that resuspends upon shaking to form a homogeneous suspension. AFLURIA QUADRIVALENT is prepared from influenza



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virus propagated in the allantoic fluid of embryonated chicken eggs. Following harvest, the virus is purified in a sucrose density gradient using continuous flow zonal centrifugation. The purified virus is inactivated with beta-propiolactone, and the virus particles are disrupted using sodium taurodeoxycholate to produce a “split virion”. The disrupted virus is further purified and suspended in a phosphate buffered isotonic solution.

AFLURIA QUADRIVALENT is standardized according to USPHS requirements for the 2019-2020 influenza season and is formulated to contain 60 mcg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA for each of the four influenza strains recommended for the 2019-2020 Northern Hemisphere influenza season:

A/Brisbane/02/2018 (IVR-190) (an A/Brisbane/02/2018 (H1N1)pdm09 – like virus), A/Kansas/14/2017 (X-327) (an A/Kansas/14/2017 (H3N2) – like virus), B/Maryland/15/2016 (a B/Colorado/06/2017 – like virus) and B/Phuket/3073/2013 BVR-1B (a B/Phuket/3073/2013 – like virus). A 0.25 mL dose contains 7.5 mcg HA of each of the same four influenza strains.

Thimerosal, a mercury derivative, is not used in the manufacturing process for the single dose presentation. This presentation does not contain preservative. The multi-dose presentation contains thimerosal added as a preservative; each 0.5 mL dose contains 24.5 mcg of mercury and each 0.25 mL dose contains 12.25 mcg of mercury.

A single 0.5 mL dose of AFLURIA QUADRIVALENT contains sodium chloride (4.1 mg), monobasic sodium phosphate (80 mcg), dibasic sodium phosphate (300 mcg), monobasic potassium phosphate (20 mcg), potassium chloride (20 mcg), and calcium chloride (0.5 mcg). From the manufacturing process, each 0.5 mL dose may also contain residual amounts of sodium taurodeoxycholate ( $\leq 10$  ppm), ovalbumin ( $< 1$  mcg), sucrose ( $< 10$  mcg), neomycin sulfate ( $\leq 81.8$  nanograms [ng]), polymyxin B ( $\leq 14$  ng), beta-propiolactone ( $\leq 1.5$  ng) and hydrocortisone ( $\leq 0.56$  ng). A single 0.25 mL dose of AFLURIA QUADRIVALENT contains half of these quantities.

The rubber tip cap and plunger used for the preservative-free, single-dose syringes and the rubber stoppers used for the multi-dose vial were not made with natural rubber latex.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977 antigenic variants of influenza A (H1N1 and H3N2) and influenza B viruses have been in global circulation. Since 2001, two distinct lineages of influenza B (Victoria and Yamagata lineages) have co-circulated worldwide. Specific levels of hemagglutination inhibition (HI) antibody titers post-vaccination with inactivated influenza vaccine have not been correlated with protection from influenza virus. In some human studies, antibody titers of 1:40 or greater have been associated with protection from influenza illness in up to 50% of subjects.<sup>2,3</sup>





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Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual change to one or more new strains in each year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the HA of four strains (i.e., typically two type A and two type B) representing the influenza viruses likely to be circulating in the U.S. during the upcoming winter.

Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination and circulating strains of influenza virus change from year to year.<sup>1</sup>

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

AFLURIA QUADRIVALENT has not been evaluated for carcinogenic or mutagenic potential, or male infertility in animals. A developmental toxicity study conducted in rats vaccinated with AFLURIA (trivalent formulation) revealed no impact on female fertility (see *Pregnancy [8.1]*).

## 14 CLINICAL STUDIES

### 14.1 Efficacy Against Laboratory-Confirmed Influenza

The efficacy of AFLURIA (trivalent formulation) is relevant to AFLURIA QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions (see *Description [11]*).

The efficacy of AFLURIA (trivalent formulation) was demonstrated in Study 5, a randomized, observer-blind, placebo-controlled study conducted in 15,044 subjects. Healthy subjects 18 through 64 years of age were randomized in a 2:1 ratio to receive a single dose of AFLURIA (trivalent formulation) (enrolled subjects: 10,033; evaluable subjects: 9,889) or placebo (enrolled subjects: 5,011; evaluable subjects: 4,960). The mean age of all randomized subjects was 35.5 years. 54.4% were female and 90.2% were White. Laboratory-confirmed influenza was assessed by active and passive surveillance of influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of the influenza season, approximately 6 months post-vaccination. ILI was defined as at least one respiratory symptom (e.g., cough, sore throat, nasal congestion) and at least one systemic symptom (e.g., oral temperature of 100.0°F or higher, feverishness, chills, body aches). Nasal and throat swabs were collected from subjects who presented with an ILI for laboratory confirmation by viral culture and real-time reverse transcription polymerase chain reaction. Influenza virus strain was further characterized using gene sequencing and pyrosequencing.

Attack rates and vaccine efficacy, defined as the relative reduction in the influenza infection rate for AFLURIA (trivalent formulation) compared to placebo, were calculated using the per protocol population. Vaccine efficacy against laboratory-confirmed influenza infection due to



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influenza A or B virus strains contained in the vaccine was 60% with a lower limit of the 95% CI of 41% (Table 6).

**Table 6: AFLURIA (trivalent formulation): Laboratory-Confirmed Influenza Infection Rate and Vaccine Efficacy in Adults 18 through 64 Years of Age (Study 5)<sup>a</sup>**

	Subjects <sup>b</sup>	Laboratory-Confirmed Influenza Cases	Influenza Infection Rate	Vaccine Efficacy <sup>c</sup>	
	N	N	n/N %	%	Lower Limit of the 95% CI
Vaccine-matched Strains					
AFLURIA	9889	58	0.59	60	41
Placebo	4960	73	1.47		
Any Influenza Virus Strain					
AFLURIA	9889	222	2.24	42	28
Placebo	4960	192	3.87		

Abbreviations: CI, confidence interval.

<sup>a</sup> NCT00562484

<sup>b</sup> The Per Protocol Population was identical to the Evaluable Population in this study.

<sup>c</sup> Vaccine efficacy = 1 minus the ratio of AFLURIA (trivalent formulation) /placebo infection rates. The objective of the study was to demonstrate that the lower limit of the CI for vaccine efficacy was greater than 40%.

## 14.2 Immunogenicity of AFLURIA QUADRIVALENT in Adults and Older Adults Administered by Needle and Syringe

Study 1 was a randomized, double-blind, active-controlled trial conducted in the U.S. in adults aged 18 years of age and older. Subjects received one dose of either AFLURIA QUADRIVALENT (N=1691) or one of two formulations of comparator trivalent influenza vaccine (AFLURIA, TIV-1 N=854 or TIV-2 N=850) each containing an influenza type B virus that corresponded to one of the two B viruses in AFLURIA QUADRIVALENT (a type B virus of the Yamagata lineage or a type B virus of the Victoria lineage, respectively).

Post-vaccination immunogenicity was evaluated on sera obtained 21 days after administration of a single dose of AFLURIA QUADRIVALENT or TIV comparator. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers) and the difference in seroconversion rates for each vaccine strain, 21 days after vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (TIV/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (TIV minus AFLURIA QUADRIVALENT) did not exceed 10.0% for each strain.

Serum HI antibody responses to AFLURIA QUADRIVALENT were non-inferior to both TIVs for all influenza strains for subjects 18 years of age and older. Additionally, non-inferiority was demonstrated for both endpoints in both age sub-groups, adults aged 18 through 64 years and 65 years and older, for all strains (Table 7). Superiority of the immune response to each of the influenza B strains contained in AFLURIA QUADRIVALENT was shown relative to the



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494 antibody response after vaccination with TIV formulations not containing that B lineage strain  
495 for subjects 18 years of age and older. Superiority against the alternate B strain was also  
496 demonstrated for each of the influenza B strains in both age sub-groups; 18 through 64 years and  
497 65 years and older. Post-hoc analyses of immunogenicity endpoints by gender did not  
498 demonstrate meaningful differences between males and females. The study population was not  
499 sufficiently diverse to assess differences between races or ethnicities.



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**Table 7: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA QUADRIVALENT Relative to Trivalent Influenza Vaccine (TIV) by Age Cohort (Study 1)<sup>a</sup>**

	Post-vaccination GMT		GMT Ratio <sup>b</sup>	Seroconversion % <sup>c</sup>		Difference	Met both pre-defined non-inferiority criteria? <sup>d</sup>
Strain	AFLURIA Quadrivalent	Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)	Pooled TIV or TIV-1 or TIV-2 over AFLURIA Quadrivalent (95% CI)	AFLURIA Quadrivalent N=1691	Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)	Pooled TIV or TIV-1 or TIV-2 minus AFLURIA Quadrivalent (95% CI)	
18 through 64 years	AFLURIA Quadrivalent N=835, Pooled TIV N=845, TIV-1 N=424, TIV-2 N=421						
A(H1N1)	432.7	402.8	0.93 <sup>e</sup> (0.85, 1.02)	51.3	49.1	-2.1 <sup>h</sup> (-6.9, 2.7)	Yes
A(H3N2)	569.1	515.1	0.91 <sup>e</sup> (0.83, 0.99)	56.3	51.7	-4.6 <sup>h</sup> (-9.4, 0.2)	Yes
B/Massachusetts/2/2012 (B Yamagata)	92.3	79.3	0.86 <sup>f</sup> (0.76, 0.97)	45.7	41.3	-4.5 <sup>i</sup> (-10.3, 1.4)	Yes
B/Brisbane/60/2008 (B Victoria)	110.7	95.2	0.86 <sup>g</sup> (0.76, 0.98)	57.6	53.0	-4.6 <sup>j</sup> (-10.5, 1.2)	Yes
≥ 65 years	AFLURIA Quadrivalent N=856, Pooled TIV N=859, TIV-1 N=430, TIV-2 N=429						
A(H1N1)	211.4	199.8	0.95 <sup>e</sup> (0.88, 1.02)	26.6	26.4	-0.2 <sup>h</sup> (-5.0, 4.5)	Yes
A(H3N2)	419.5	400.0	0.95 <sup>e</sup> (0.89, 1.02)	25.9	27.0	1.1 <sup>h</sup> (-3.7, 5.8)	Yes
B/Massachusetts/2/2012 (B Yamagata)	43.3	39.1	0.90 <sup>f</sup> (0.84, 0.97)	16.6	14.4	-2.2 <sup>i</sup> (-8.0, 3.6)	Yes
B/Brisbane/60/2008 (B Victoria)	66.1	68.4	1.03 <sup>g</sup> (0.94, 1.14)	23.5	24.7	1.2 <sup>j</sup> (-4.6, 7.0)	Yes

Abbreviations: CI, confidence interval; GMT, geometric mean titer.

<sup>a</sup> NCT02214225

<sup>b</sup> GMT ratio was computed after fitting a multi-variable model on the post-vaccination titers including sex, vaccination history, pre-vaccination HI titers and other factors.

<sup>c</sup> Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer  $\geq 1:10$  or an increase in titer from  $< 1:10$  to  $\geq 1:40$ .

<sup>d</sup> Non-inferiority (NI) criterion for the GMT ratio: upper bound of 2-sided 95% CI on the GMT ratio of Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)/AFLURIA Quadrivalent should not exceed 1.5. NI criterion for the SCR difference: upper bound of 2-sided 95% CI on the difference between SCR Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria) minus AFLURIA Quadrivalent should not exceed 10%.

<sup>e</sup> Pooled TIV/AFLURIA Quadrivalent

<sup>f</sup> TIV-1 (B Yamagata)/AFLURIA Quadrivalent

<sup>g</sup> TIV-2 (B Victoria)/AFLURIA Quadrivalent

<sup>h</sup> Pooled TIV - AFLURIA Quadrivalent

<sup>i</sup> TIV-1 (B Yamagata) - AFLURIA Quadrivalent

<sup>j</sup> TIV-2 (B Victoria) - AFLURIA Quadrivalent



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### 14.3 Immunogenicity of AFLURIA (trivalent formulation) Administered by PharmaJet Stratis Needle-Free Injection System

Study 2 was a randomized, comparator-controlled, non-inferiority study that enrolled 1,250 subjects 18 through 64 years of age. This study compared the immune response following administration of AFLURIA (trivalent formulation) when delivered intramuscularly using either the PharmaJet Stratis Needle-Free Injection System or needle and syringe. Immunogenicity assessments were performed prior to vaccination and at 28 days after vaccination in the immunogenicity population (1130 subjects, 562 PharmaJet Stratis Needle-Free Injection System group, 568 needle and syringe group). The co-primary endpoints were HI GMT ratios for each vaccine strain and the absolute difference in seroconversion rates for each vaccine strain 28 days after vaccination. As shown in Table 8, non-inferiority of administration of AFLURIA (trivalent formulation) by the PharmaJet Stratis Needle-Free Injection System compared to administration of AFLURIA (trivalent formulation) by needle and syringe was demonstrated in the immunogenicity population for all strains. Post-hoc analyses of immunogenicity by age showed that younger subjects (18 through 49 years) elicited higher immunological responses than older subjects (50 through 64 years). Post-hoc analyses of immunogenicity according to sex and body mass index did not reveal significant influences of these variables on immune responses. The study population was not sufficiently diverse to assess immunogenicity by race or ethnicity.

**Table 8: Baseline and Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA (trivalent formulation) Administered by PharmaJet Stratis Needle-Free Injection System or Needle and Syringe, Adults 18 through 64 Years of Age (Study 2)<sup>a</sup>**

Strain	Baseline GMT		Post-vaccination GMT		GMT Ratio <sup>b</sup>	Seroconversion % <sup>c</sup>		Difference Needle and Syringe minus PharmaJet Stratis Needle-Free Injection System (95% CI)	Met both pre-defined non- inferiority criteria? <sup>d</sup>
	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562		Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562		
A(H1N1)	79.5	83.7	280.6	282.9	0.99 (0.88, 1.12)	38.4	37.5	0.8 (-4.8, 6.5)	Yes
A(H3N2)	75.4	68.1	265.9	247.3	1.08 (0.96, 1.21)	45.1	43.8	1.3 (-4.5, 7.1)	Yes
B	12.6	13.5	39.7	42.5	0.94 (0.83, 1.06)	35.2	34.9	0.3 (-5.2, 5.9)	Yes

Abbreviations: CI, confidence interval; GMT, geometric mean titer.

<sup>a</sup> NCT01688921

<sup>b</sup> GMT ratio is defined as post-vaccination GMT for Needle and Syringe/PharmaJet Stratis Needle-Free Injection System.

<sup>c</sup> Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer  $\geq 1:10$  or an increase in titer from  $< 1:10$  to  $\geq 1:40$ .

<sup>d</sup> Non-inferiority (NI) criterion for the GMT ratio: upper bound of 2-sided 95% CI on the GMT ratio of Needle and Syringe/PharmaJet Stratis Needle-Free Injection System should not exceed 1.5. NI criterion for the seroconversion rate (SCR) difference: upper bound of 2-sided 95% CI on the difference between SCR Needle and Syringe – SCR PharmaJet Stratis Needle-Free Injection System should not exceed 10%.



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**14.4 Immunogenicity of AFLURIA QUADRIVALENT in Children 5 through 17 Years Administered by Needle and Syringe**

Study 3 was a randomized, observer-blinded, comparator-controlled trial conducted in the U.S. in children 5 through 17 years of age. A total of 2278 subjects were randomized 3:1 to receive one or two doses of AFLURIA QUADRIVALENT (N=1709) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=569). Subjects 5 through 8 years of age were eligible to receive a second dose at least 28 days after the first dose depending on their influenza vaccination history, consistent with the 2015-2016 recommendations of the Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal Influenza with Vaccines. Approximately 25% of subjects in each treatment group in the 5 through 8 years of age subgroup received two vaccine doses.

Baseline serology for HI assessment was collected prior to vaccination. Post-vaccination immunogenicity was evaluated by HI assay on sera obtained 28 days after the last vaccination dose.

The primary objective was to demonstrate that vaccination with AFLURIA QUADRIVALENT elicits an immune response that is not inferior to that of a comparator vaccine containing the same recommended virus strains. The Per Protocol Population (AFLURIA QUADRIVALENT n=1605, Comparator n=528) was used for the primary endpoint analyses. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (Comparator/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator minus AFLURIA QUADRIVALENT) did not exceed 10.0% for each strain. Serum HI antibody responses to AFLURIA QUADRIVALENT were non-inferior for both GMT ratio and seroconversion rates relative to the comparator vaccine for all influenza strains (Table 9). Analyses of immunogenicity endpoints by gender did not demonstrate meaningful differences between males and females. The study population was not sufficiently diverse to assess differences among races or ethnicities.



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**Table 9: Post-Vaccination HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority of AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator Quadrivalent Influenza Vaccine for each Strain 28 Days after Last Vaccination Among a Pediatric Population 5 through 17 Years of Age (Per Protocol Population) (Study 3)<sup>a,b</sup>**

	Post-vaccination GMT		GMT Ratio <sup>c</sup>	Seroconversion % <sup>d</sup>		SCR Difference <sup>e</sup>	Met both pre-defined non-inferiority criteria? <sup>f</sup>
Strain	AFLURIA Quadrivalent N=1605	Comparator N=528	Comparator over AFLURIA Quadrivalent (95% CI)	AFLURIA Quadrivalent N=1605 (95% CI)	Comparator N=528 (95% CI)	Comparator minus AFLURIA Quadrivalent (95% CI)	
A(H1N1)	952.6 (n=1604 <sup>g</sup> )	958.8	1.01 (0.93, 1.09)	66.4 (64.0, 68.7)	63.3 (59.0, 67.4)	-3.1 (-8.0, 1.8)	Yes
A(H3N2)	886.4 (n=1604 <sup>g</sup> )	930.6	1.05 (0.96, 1.15)	82.9 (81.0, 84.7)	83.3 (79.9, 86.4)	0.4 (-4.5, 5.3)	Yes
B/Phuket/3073/2013 (B Yamagata)	60.9 (n=1604 <sup>g</sup> )	54.3	0.89 (0.81, 0.98)	58.5 (56.0, 60.9)	55.1 (50.8, 59.4)	-3.4 (-8.3, 1.5)	Yes
B/Brisbane/60/2008 (B Victoria)	145.0 (n=1604 <sup>g</sup> )	133.4	0.92 (0.83, 1.02)	72.1 (69.8, 74.3)	70.1 (66.0, 74.0)	-2.0 (-6.9, 2.9)	Yes

Abbreviations: CI, confidence interval; Comparator, Comparator quadrivalent influenza vaccine (Fluarix<sup>®</sup> Quadrivalent [GlaxoSmithKline Biologicals]); GMT (adjusted), geometric mean titer; SCR, seroconversion rate.

<sup>a</sup> NCT02545543

<sup>b</sup> The Per-Protocol Population comprised all subjects in the Evaluable Population who did not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results.

<sup>c</sup> GMT Ratio = Comparator /AFLURIA QUADRIVALENT. Adjusted analysis model: Log-transformed Post-Vaccination HI Titer=Vaccine + Age Strata [5-8, 9-17] + Gender + Vaccination History [y/n] + Log-transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Strata\*Vaccine. The Age Strata\*Vaccine interaction term was excluded from the model fit for the strains B/Yamagata and B/Victoria as the interaction result was non-significant (p>0.05). Least square means were back transformed.

<sup>d</sup> Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.

<sup>e</sup> Seroconversion rate difference = Comparator SCR percentage minus AFLURIA QUADRIVALENT SCR percentage.

<sup>f</sup> Non-inferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator /AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95% CI on the difference between SCR Comparator – AFLURIA QUADRIVALENT should not exceed 10%.

<sup>g</sup> Subject 8400394-0046 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio since the subject did not have information on all covariates (unknown prevaccination history).

## 14.5 Immunogenicity of AFLURIA QUADRIVALENT in Children 6 Months through 59 Months Administered by Needle and Syringe

Study 4 was a randomized, observer-blind, comparator-controlled trial conducted in the U.S. in children 6 months through 59 months of age. A total of 2247 subjects were randomized 3:1 to receive AFLURIA QUADRIVALENT (N=1684) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=563). Children 6 months through 35 months received one or two 0.25 mL doses and children 36 months through 59 months received one or two 0.5 mL doses. Subjects were eligible to receive a second dose at least 28 days after the first dose depending on their influenza vaccination history, consistent with the 2016-2017 recommendations of the Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal

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612 Influenza with Vaccines. Approximately 40% of subjects in each treatment group received two  
613 vaccine doses.

614 Baseline serology for HI assessment was collected prior to vaccination. Postvaccination  
615 immunogenicity was evaluated by HI assay on sera obtained 28 days after the last vaccination  
616 dose.

617 The primary objective was to demonstrate that vaccination with AFLURIA QUADRIVALENT  
618 elicits an immune response that is not inferior to that of a comparator vaccine containing the  
619 same recommended virus strains. The Per Protocol Population (AFLURIA QUADRIVALENT  
620 n=1456, Comparator QIV n=484) was used for the primary endpoint analyses. The co-primary  
621 endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other  
622 covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination.  
623 Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the  
624 GMT ratio (Comparator QIV/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper  
625 bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator QIV minus  
626 AFLURIA QUADRIVALENT) did not exceed 10.0% for each strain. Serum HI antibody  
627 responses to AFLURIA QUADRIVALENT were non-inferior for both GMT ratio and  
628 seroconversion rates relative to the comparator vaccine for all influenza strains (Table 10).  
629 Analyses of immunogenicity endpoints by gender did not demonstrate meaningful differences  
630 between males and females. The study population was not sufficiently diverse to assess  
631 differences among races or ethnicities.





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**Table 10: Post-Vaccination HI Antibody GMTs, SCR, and Analyses of Non-Inferiority of AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator Quadrivalent Influenza Vaccine for each Strain 28 Days after Last Vaccination Among a Pediatric Population 6 through 59 Months of Age (Per Protocol Population) (Study 4)<sup>a, b</sup>**

Strain	Post-vaccination GMT		GMT Ratio <sup>c</sup>	Seroconversion % <sup>d</sup>		SCR Difference <sup>e</sup> Comparator minus AFLURIA Quadrivalent (95% CI)	Met both pre-defined non- inferiority criteria? <sup>f</sup>
	AFLURIA Quadrivalent N=1456	Comparator N=484		AFLURIA Quadrivalent N=1456 (95% CI)	Comparator N=484 (95% CI)		
A(H1N1)	353.5 (n=1455 <sup>g</sup> )	281.0 (n=484)	0.79 (0.72, 0.88)	79.1 (76.9, 81.1) (n=1456)	68.8 (64.5, 72.9) (n=484)	-10.3 (-15.4, -5.1)	Yes
A(H3N2)	393.0 (n=1454 <sup>g</sup> )	500.5 (n=484)	1.27 (1.15, 1.42)	82.3 (80.2, 84.2) (n=1455 <sup>h</sup> )	84.9 (81.4, 88.0) (n=484)	2.6 (-2.5, 7.8)	Yes
B/Phuket/3073/ 2013 (B Yamagata)	23.7 (n=1455 <sup>g</sup> )	26.5 (n=484)	1.12 (1.01, 1.24)	38.9 (36.4, 41.4) (n=1456)	41.9 (37.5, 46.5) (n=484)	3.1 (-2.1, 8.2)	Yes
B/Brisbane/60/ 2008 (B Victoria)	54.6 (n=1455 <sup>g</sup> )	52.9 (n=483 <sup>h</sup> )	0.97 (0.86, 1.09)	60.2 (57.6, 62.7) (n=1456)	61.1 (56.6, 65.4) (n=483 <sup>h</sup> )	0.9 (-4.2, 6.1)	Yes

Abbreviations: CI, confidence interval; Comparator, Comparator quadrivalent influenza vaccine (Fluzone Quadrivalent [Sanofi Aventis]); GMT (adjusted), geometric mean titer; SCR, seroconversion rate.

<sup>a</sup> NCT02914275

<sup>b</sup> The Per-Protocol Population comprised all subjects (6 through 35 months of age receiving one or two 0.25 mL doses and 36 through 59 months of age receiving one or two 0.5 mL doses) in the Evaluable Population who did not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results.

<sup>c</sup> GMT Ratio = Comparator / AFLURIA QUADRIVALENT. Adjusted analysis model: Log-transformed Post-Vaccination HI Titer = Vaccine + Age Cohort [6 through 35 months or 36 through 59 months] + Gender + Vaccination History [y/n] + Log-transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Cohort\*Vaccine. The Age Cohort\*Vaccine interaction term was excluded from the model fit for the strains A(H1N1), A(H3N2) and B/Yamagata as the interaction result was non-significant (p>0.05). Least square means were back transformed.

<sup>d</sup> Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.

<sup>e</sup> Seroconversion rate difference = Comparator SCR percentage minus AFLURIA QUADRIVALENT SCR percentage.

<sup>f</sup> Noninferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator / AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95% CI on the difference between SCR Comparator – AFLURIA QUADRIVALENT should not exceed 10%.

<sup>g</sup> Subject 8400402-0073 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio because the subject did not have information on all covariates (unknown prevaccination history).

<sup>h</sup> Subject 8400427-0070 had missing B/Victoria Antigen pre-vaccination titer.

<sup>i</sup> Subject 8400402-0074 had missing A/H3N2 post-vaccination titer.

## 15 REFERENCES

- Centers for Disease Control and Prevention. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2010;59 (RR-8):1-62.
- Hannoun C, Megas F, Piercy J. Immunogenicity and Protective Efficacy of Influenza Vaccination. *Virus Res* 2004;103:133-138.
- Hobson D, Curry RL, Beare AS, et al. The Role of Serum Hemagglutination-Inhibiting Antibody in Protection against Challenge Infection with Influenza A2 and B Viruses. *J Hyg Camb* 1972;70:767-777.



**Package insert****16 HOW SUPPLIED/STORAGE AND HANDLING****16.1 How Supplied**

Each product presentation includes a package insert and the following components:

Presentation	Carton NDC Number	Components
Pre-Filled Syringe	33332-219-20	<ul style="list-style-type: none"> <li>Ten 0.25 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-219-21]</li> </ul>
Pre-Filled Syringe	33332-319-01	<ul style="list-style-type: none"> <li>Ten 0.5 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-319-02]</li> </ul>
Multi-Dose Vial	33332-419-10	<ul style="list-style-type: none"> <li>One 5 mL vial [NDC 33332-419-11]</li> </ul>

**16.2 Storage and Handling**

- Store refrigerated at 2–8°C (36–46°F).
- Do not freeze. Discard if product has been frozen.
- Protect from light.
- Do not use AFLURIA QUADRIVALENT beyond the expiration date printed on the label.
- Between uses, return the multi-dose vial to the recommended storage conditions.
- Once the stopper of the multi-dose vial has been pierced the vial must be discarded within 28 days.
- No more than 10 doses (0.25 mL or 0.5 mL) should be withdrawn from the multi-dose vial.

**17 PATIENT COUNSELING INFORMATION**

- Inform the vaccine recipient or guardian of the potential benefits and risks of immunization with AFLURIA QUADRIVALENT.
- Inform the vaccine recipient or guardian that AFLURIA QUADRIVALENT is an inactivated vaccine that cannot cause influenza but stimulates the immune system to produce antibodies that protect against influenza, and that the full effect of the vaccine is generally achieved approximately 3 weeks after vaccination.
- Instruct the vaccine recipient or guardian to report any severe or unusual adverse reactions to their healthcare provider.
- Encourage women who receive AFLURIA QUADRIVALENT while pregnant to enroll in the pregnancy registry. Pregnant women can enroll in the pregnancy registry by calling 1-855-358-8966 or sending an email to Seqirus at [us.medicalinformation@seqirus.com](mailto:us.medicalinformation@seqirus.com).
- Provide the vaccine recipient Vaccine Information Statements prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).
- Instruct the vaccine recipient that annual revaccination is recommended.



**Package insert**

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698 Manufactured by:  
699 **Seqirus Pty Ltd.** Parkville, Victoria, 3052, Australia  
700 U.S. License No. 2044

701 Distributed by:  
702 **Seqirus USA Inc.** 25 Deforest Avenue, Summit, NJ 07901, USA  
703 1-855-358-8966

704 AFLURIA is a registered trademark of Seqirus UK Limited or its affiliates.  
705 PharmaJet® and STRATIS® are registered trademarks of PharmaJet.  
706 Luer-Lok™ is a trademark of Becton, Dickinson and Company Corporation.

# **EXHIBIT 267**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLUCELVAX® QUADRIVALENT safely and effectively. See full prescribing information for FLUCELVAX QUADRIVALENT.

### FLUCELVAX QUADRIVALENT (Influenza Vaccine)

#### Suspension for Intramuscular Injection

2019-2020 Formula

Initial U.S. Approval: 23 May 2016

## INDICATIONS AND USAGE

FLUCELVAX QUADRIVALENT is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. (1)

(1) FLUCELVAX is approved for use in persons 4 years of age and older. (1)

For children and adolescents 4 through 17 years of age, approval is based on the immune response elicited by FLUCELVAX QUADRIVALENT. Data demonstrating a decrease in influenza disease after vaccination of children and adolescents 4 through 17 years of age with FLUCELVAX QUADRIVALENT are not available. (14)

## DOSAGE AND ADMINISTRATION

### For intramuscular use only

Age	Dose	Schedule
4 through 8 years of age	One or two doses <sup>a</sup> , 0.5 mL each	If 2 doses, administer at least 4 weeks apart
9 years of age and older	One dose, 0.5mL	Not Applicable

<sup>a</sup> 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

## DOSAGE FORMS AND STRENGTHS

Suspension for injection supplied in two presentations:

- 0.5-mL single-dose pre-filled syringes. (3,11)
- 5 mL multi-dose vial containing 10 doses (each dose is 0.5mL). (3,11)

## CONTRAINDICATIONS

History of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine. (4, 11)

## FULL PRESCRIBING INFORMATION: CONTENTS\*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
  - 2.1 Dosage and Schedule
  - 2.2 Administration
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
  - 5.1 Guillain-Barré Syndrome
  - 5.2 Preventing and Managing Allergic Reactions
  - 5.3 Syncope
  - 5.4 Altered Immunocompetence
  - 5.5 Limitations of Vaccine Effectiveness
- 6 ADVERSE REACTIONS

## WARNINGS AND PRECAUTIONS

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLUCELVAX QUADRIVALENT should be based on careful consideration of the potential benefits and risks. (5.1)

## ADVERSE REACTIONS

- The most common (≥10%) local and systemic reactions in adults 18-64 years of age were injection site pain (45.4%), headache (18.7%), fatigue (17.8%) and myalgia (15.4%), injection site erythema (13.4%), and induration (11.6%). (6)
- The most common (≥10%) local and systemic reactions in adults ≥65 years of age were injection site pain (21.6%) and injection site erythema (11.9%). (6)
- The most common (≥10%) local and systemic reactions in children 4 to <6 years of age were tenderness at the injection site (46%), injection site erythema (18%), sleepiness (19%), irritability (16%), injection site induration (13%) and change in eating habits (10%). (6)
- The most common (≥10%) local and systemic reactions in children 6 through 8 years of age were pain at the injection site (54%), injection site erythema (22%), injection site induration (16%), headache (14%), fatigue (13%) and myalgia (12%). (6)
- The most common (≥10%) local and systemic reactions in children and adolescents 9 through 17 years of age were pain at the injection site (58%), headache (22%), injection site erythema (19%), fatigue (18%) myalgia (16%), and injection site induration (15%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Seqirus at 1-855-358-8966 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

## USE IN SPECIFIC POPULATIONS

- Geriatric Use: Antibody responses were lower in adults 65 years and older than in younger adults. (8.5)
- Pregnancy: There is a pregnancy exposure registry that monitors outcomes in women exposed to FLUCELVAX QUADRIVALENT during pregnancy. Enroll in the pregnancy registry by calling 1-855-358-8966 or sending an email to [us.medicalinformation@seqirus.com](mailto:us.medicalinformation@seqirus.com). (8.1)

See 17 for PATIENT COUNSELING INFORMATION  
Revised: 04/2019

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

## 8 USE IN SPECIFIC POPULATIONS

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- 8.2 Lactation
- 8.4 Pediatric Use
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\*Sections or subsections omitted from the full prescribing information are not listed

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

FLUCELVAX QUADRIVALENT is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUCELVAX QUADRIVALENT is approved for use in persons 4 years of age and older. For children and adolescents 4 through 17 years of age, approval is based on the immune response elicited by FLUCELVAX QUADRIVALENT. Data demonstrating a decrease in influenza disease after vaccination of this age group with FLUCELVAX QUADRIVALENT are not available. *[see Clinical Studies (14)]*

### 2 DOSAGE AND ADMINISTRATION

**For intramuscular injection only.**

#### 2.1 Dosage and Schedule

Administer FLUCELVAX QUADRIVALENT as a single 0.5 mL intramuscular injection preferably in the region of the deltoid muscle of the upper arm. Do not inject the vaccine in the gluteal region or areas where there may be a major nerve trunk.

Table 1: Dosage and Schedule

Age	Dose	Schedule
4 through 8 years of age	One or two doses <sup>1</sup> , 0.5 mL each	If 2 doses, administer at least 4 weeks apart
9 years of age and older	One dose, 0.5mL	Not Applicable

<sup>1</sup> 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

#### 2.2 Administration

**Shake the syringe vigorously before administering and shake the multi-dose vial preparation each time before withdrawing a dose of vaccine. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. *[see Description (11)]* If either condition exists, do not administer the vaccine. Between uses, return the multi-dose vial to the recommended storage conditions between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen.**

**Attach a sterile needle to the pre-filled syringe.**

For the multi-dose vial, a separate sterile syringe and needle must be used for each injection to prevent transmission of infectious agents from one person to another. Needles should be disposed of properly and not recapped. It is recommended that small syringes (0.5 mL or 1 mL) should be used to minimize any product loss.

**Administer intramuscularly only. Do not administer this product intravenously, intradermally or subcutaneously.**

### **3 DOSAGE FORMS AND STRENGTHS**

FLUCELVAX QUADRIVALENT is a suspension for injection supplied in two presentations:

- a 0.5 mL single-dose pre-filled Luer Lock syringe
- a 5 mL multi-dose vial containing 10 doses (each dose is 0.5 mL).

### **4 CONTRAINDICATIONS**

Do not administer FLUCELVAX QUADRIVALENT to anyone with a history of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine [*see Description (11)*].

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Guillain-Barré Syndrome**

The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated.<sup>1</sup> If GBS has occurred after receipt of a prior influenza vaccine, the decision to give FLUCELVAX QUADRIVALENT should be based on careful consideration of the potential benefits and risks.

#### **5.2 Preventing and Managing Allergic Reactions**

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

#### **5.3 Syncope**

Syncope (fainting) can occur in association with administration of injectable vaccines, including Flucelvax. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope by maintaining a supine or Trendelenburg position.

#### **5.4 Altered Immunocompetence**

After vaccination with FLUCELVAX QUADRIVALENT, immunocompromised individuals, including those receiving immunosuppressive therapy, may have a reduced immune response.

#### **5.5 Limitations of Vaccine Effectiveness**

Vaccination with FLUCELVAX QUADRIVALENT may not protect all vaccine recipients against influenza disease.

### **6 ADVERSE REACTIONS**

#### **6.1 Clinical Trials Experience**

The most common ( $\geq 10\%$ ) local and systemic reactions in adults 18 through 64 years of age were injection site pain (45.4%), headache (18.7%), fatigue (17.8%) and myalgia (15.4%), injection site erythema (13.4%), and induration (11.6%).



**The most common ( $\geq 10\%$ ) local and systemic reactions in adults  $\geq 65$  years of age were injection site pain (21.6%), and injection site erythema (11.9%).**

**The most common ( $\geq 10\%$ ) local and systemic reactions in children 4 through 5 years of age after first dose of vaccine were tenderness at the injection site (46%), injection site erythema (18%), sleepiness (19%), irritability (16%), injection site induration (13%) and change in eating habits (10%).**

**The most common ( $\geq 10\%$ ) local and systemic reactions in children 6 through 8 years of age after first dose of vaccine were pain at the injection site (54%), injection site erythema (22%), injection site induration (16%), headache (14%), fatigue (13%) and myalgia (12%).**

**The most common ( $\geq 10\%$ ) local and systemic reactions in children and adolescents 9 through 17 years of age were pain at the injection site (58%), headache (22%), injection site erythema (19%), fatigue (18%) and myalgia (16%), and injection site induration (15%).**

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a vaccine cannot be directly compared to rates in clinical studies of another vaccine, and may not reflect rates observed in clinical practice.

Adults 18 years of age and older:

The safety of FLUCELVAX QUADRIVALENT in adults was evaluated in a randomized, double-blind, controlled study conducted in the US (Study 1). The safety population included a total of 2680 adults 18 years of age and older; 1340 adults 18 through 64 years of age and 1340 adults 65 years of age and older.

In this study, subjects received FLUCELVAX QUADRIVALENT or one of the two formulations of comparator trivalent influenza vaccine (TIV1c and TIV2c) (FLUCELVAX QUADRIVALENT (n=1335), TIV1c, n=676 or TIV2c, n= 669). The mean age of subjects who received FLUCELVAX QUADRIVALENT was 57.4 years of age; 54.8% of subjects were female and 75.6% were Caucasian, 13.4% were Black, 9.1% were Hispanics, 0.7% were American Indian and 0.3%, 0.1% and 0.7% were Asian, Native Hawaiian and others, respectively. The safety data observed are summarized in Table 2.

In this study, solicited local injection site and systemic adverse reactions were collected from subjects who completed a symptom diary card for 7 days following vaccination.

Solicited adverse reactions for FLUCELVAX QUADRIVALENT and comparator are summarized in Table 2.

**Table 2: Incidence of Solicited Adverse Reactions in the Safety Population<sup>1</sup> Reported Within 7 Days of Vaccination (Study 1)**

	18 through 64 years of age			≥ 65 years of age		
	Percentages (%) <sup>2</sup>					
	FLUCELVAX QUADRIVALENT N=663	Trivalent Influenza Vaccine		FLUCELVAX QUADRIVALENT N=656	Trivalent Influenza Vaccine	
TIV1c N=330		TIV2c N=327	TIV1c N=340		TIV2c N=336	
Local Adverse Reactions						
Injection site induration	11.6 (0)	9.7 (0.3)	10.4 (0)	8.7 (0)	6.8 (0)	7.7 (0)
Injection site erythema	13.4 (0)	13.3 (0)	10.1 (0)	11.9 (0)	10.6 (0)	10.4 (0)
Injection site ecchymosis	3.8 (0)	3.3 (0.3)	5.2 (0)	4.7 (0)	4.4 (0)	5.4 (0)
Injection site pain	45.4 (0.5)	37.0 (0.3)	40.7 (0)	21.6 (0)	18.8 (0)	18.5 (0)
Systemic Adverse Reactions						
Chills	6.2 (0.2)	6.4 (0.6)	6.4 (0)	4.4 (0.3)	4.1 (0.3)	4.5 (0.6)
Nausea	9.7 (0.3)	7.3 (0.9)	8.9 (1.2)	3.8 (0.2)	4.1 (0)	4.2 (0.3)
Myalgia	15.4 (0.8)	14.5 (0.9)	15.0 (1.2)	8.2 (0.2)	9.4 (0.3)	8.3 (0.6)
Arthralgia	8.1 (0.5)	8.2 (0)	9.5 (0.9)	5.5 (0.5)	5.0 (0.3)	6.8 (0.9)
Headache	18.7 (0.9)	18.5 (0.9)	18.7 (0.6)	9.3 (0.3)	8.5 (0.6)	8.3 (0.6)
Fatigue	17.8 (0.6)	22.1 (0.3)	15.6 (1.5)	9.1 (0.8)	10.6 (0.3)	8.9 (0.6)
Vomiting	2.6 (0)	1.5 (0.3)	0.9 (0)	0.9 (0.2)	0.3 (0)	0.6 (0)
Diarrhea	7.4 (0.6)	7.6 (0)	7.6 (0.6)	4.3 (0.5)	5.0 (0.9)	5.1 (0.3)
Loss of appetite	8.3 (0.3)	8.5 (0.3)	8.3 (0.9)	4.0 (0.2)	5.0 (0)	3.6 (0.3)
Fever: ≥38.0 °C (>40.0 °C)	0.8 (0)	0.6 (0)	0.3 (0)	0.3 (0)	0.9 (0)	0.6 (0)

<sup>1</sup>Safety population: all subjects in the exposed population who provided post-vaccination safety data

<sup>2</sup>Percentage of severe adverse reactions are presented in parenthesis  
 Study 1: NCT01992094

Unsolicited adverse events were collected for 21 days after vaccination. In adults 18 years of age and older, unsolicited adverse events were reported in 16.1% of subjects who received FLUCELVAX QUADRIVALENT, within 21 days after vaccination.

In adults 18 years of age and older, serious adverse events (SAEs) were collected throughout the study duration (until 6 months after vaccination) and were reported by 3.9%, of the subjects who received FLUCELVAX QUADRIVALENT. None of the SAEs were assessed as being related to study vaccine.

Children and Adolescents 4 through 17 years of age:

The safety of FLUCELVAX QUADRIVALENT in children was evaluated in a randomized, double-blind, controlled study conducted in the US (Study 2). The safety population included

a total of 2332 children 4 through 17 years of age; 1161 children 4 through 8 years of age and 1171 children 9 through 17 years of age.

In this study, subjects received FLUCELVAX QUADRIVALENT or one of the two formulations of comparator trivalent influenza vaccine (FLUCELVAX QUADRIVALENT n=1159, TIV1c, n=593 or TIV2c, n= 580). Children 9 through 17 years of age received a single dose of FLUCELVAX QUADRIVALENT or comparator vaccine. Children 4 through 8 years of age received one or two doses (separated by 4 weeks) of FLUCELVAX QUADRIVALENT or comparator vaccine based on determination of the subject's prior influenza vaccination history. The mean age of subjects who received FLUCELVAX QUADRIVALENT was 9.6 years of age; 48% of subjects were female and 53% were Caucasian. The safety data observed are summarized in Table 3 and Table 4.

In this study, solicited local injection site and systemic adverse reactions were collected from subjects who completed a symptom diary card for 7 days following vaccination.

Solicited adverse reactions for FLUCELVAX QUADRIVALENT and comparator are summarized in Table 3 and Table 4.

Table 3: Incidence of Solicited Adverse Reactions in the Safety Population<sup>1</sup> (4 through 5 years of age) Reported Within 7 Days of the First dose of Vaccination (Study 2)

	Children 4 through 5 years		
	Percentages (%) <sup>2</sup>		
	FLUCELVAX QUADRIVALENT N=182	Trivalent Influenza Vaccine	
		TIV1c N=91	TIV2c N=93
<b>Local Adverse Reactions</b>			
Injection site induration	13 (1)	20 (2)	13 (0)
Injection site erythema	18 (1)	23 (1)	17 (0)
Injection site ecchymosis	9 (0)	11 (0)	8 (0)
Injection site tenderness	46 (1)	45 (1)	43 (0)
<b>Systemic Adverse Reactions</b>			
Change in eating habits	10 (1)	7	6
Sleepiness	19 (1)	12 (3)	10 (0)
Irritability	16 (2)	10 (2)	10 (1)
Chills	5 (1)	2 (0)	1 (0)
Vomiting	4 (0)	2 (0)	2 (0)
Diarrhea	4 (0)	2 (0)	2 (0)
Fever: $\geq 38.0^{\circ}\text{C}$ ( $\geq 40.0^{\circ}\text{C}$ )	4 (0)	4 (0)	3 (0)

<sup>1</sup>Safety population: all subjects in the exposed population who provided post-vaccination safety data.

<sup>2</sup>Percentage of subjects with severe adverse reactions are presented in parenthesis.

Study 2: NCT01992107

**Table 4: Incidence of Solicited Adverse Reactions in the Safety Population<sup>1</sup> (Children 6 through 17 years of age) Reported Within 7 Days of Vaccination (Study 2)**

	Children 6 through 8 years (after first dose)			Children 9 through 17 years		
	Percentages (%) <sup>2</sup>					
	FLUCELVAX QUADRIVAL ENT N=371-372	Trivalent Influenza vaccine		FLUCELVAX QUADRIVAL ENT N=579	Trivalent Influenza Vaccine	
		TIV1c N=185	TIV2c N=186		TIV1c N=294	TIV2c N=281-282
Local Adverse Reactions						
Injection site induration	16 (0)	19 (1)	13 (0)	15 (0)	15 (0)	13 (<1)
Injection site erythema	22 (0)	23 (1)	20 (0)	19 (<1)	17 (0)	15 (<1)
Injection site ecchymosis	9 (0)	9 (0)	8 (0)	4 (0)	5 (0)	5 (0)
Injection site pain	54 (1)	57 (1)	58 (2)	58 (1)	51(<1)	50 (0)
Systemic Adverse Reactions						
Chills	4 (1)	3 (0)	4 (0)	7 (0)	6 (1)	4 (1)
Nausea	8 (1)	5 (0)	5 (1)	9 (<1)	8 (1)	7 (1)
Myalgia	12 (1)	14 (0)	10 (0)	16 (<1)	17 (<1)	15 (<1)
Arthralgia	4 (0)	5 (0)	4 (0)	6 (0)	6 (0)	8 (<1)
Headache	14 (1)	13 (0)	12 (0)	22 (1)	23 (2)	18 (1)
Fatigue	13 (2)	14 (0)	18 (0)	18 (<1)	16 (1)	16 (<1)
Vomiting	3 (1)	3 (0)	3 (0)	2 (0)	1 (0)	2 (0)
Diarrhea	3 (<1)	6 (1)	5 (0)	4 (0)	4 (0)	3 (<1)
Loss of appetite	9 (<1)	5 (0)	8 (1)	9 (0)	9 (<1)	9 (0)
Fever: ≥38.0 °C (≥40.0 °C)	4 (0)	3 (0)	2 (0)	1 (<1)	3 (0)	1 (0)

<sup>1</sup>Safety population: all subjects in the exposed population who provided post-vaccination safety data.

<sup>2</sup>Percentage of subjects with severe adverse reactions are presented in parenthesis.  
Study 2: NCT 01992107

In children who received a second dose of FLUCELVAX QUADRIVALENT, TIV1c, or TIV2c, the incidence of adverse reactions following the second dose of vaccine were similar to those observed with the first dose.

Unsolicited adverse events were collected for 21 days after last vaccination. In children 4 through 17 years of age, unsolicited adverse events were reported in 24.3% of subjects who received FLUCELVAX QUADRIVALENT, within 3 weeks after last vaccination. In children 4 through 17 years of age, serious adverse events (SAEs) were collected throughout the study duration (until 6 months after last vaccination) and were reported by

0.5% of the subjects who received FLUCELVAX QUADRIVALENT. None of the SAEs were assessed as being related to study vaccine.

## 6.2 Postmarketing Experience

**The following additional adverse events have been identified during post-approval use of FLUCELVAX QUADRIVALENT. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.**

*Immune system disorders:* Allergic or immediate hypersensitivity reactions, including anaphylactic shock.

*Nervous systems disorders:* Syncope, presyncope, paresthesia.

*Skin and subcutaneous tissue disorders:* Generalized skin reactions including pruritus, urticaria or non-specific rash.

General disorders and administration site conditions: Extensive swelling of injected limb.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FLUCELVAX QUADRIVALENT during pregnancy. Women who are vaccinated with FLUCELVAX QUADRIVALENT during pregnancy are encouraged to enroll in the registry by calling 1-855-358-8966 or sending an email to Seqirus at [us.medicalinformation@seqirus.com](mailto:us.medicalinformation@seqirus.com).

#### Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are insufficient data for FLUCELVAX QUADRIVALENT in pregnant women to inform vaccine-associated risks in pregnancy.

There were no developmental toxicity studies of FLUCELVAX QUADRIVALENT performed in animals. A developmental toxicity study has been performed in female rabbits administered FLUCELVAX (trivalent formulation) prior to mating and during gestation. The dose was 0.5 mL on each occasion (a single human dose is 0.5 mL). This study revealed no evidence of harm to the fetus due to FLUCELVAX (trivalent formulation) (*see 8.1 Data*).

#### Clinical Considerations

Disease-associated Maternal and/or Embryo-Fetal Risk

Pregnant women are at increased risk for severe illness due to influenza compared to non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

#### Data

##### Animal Data

In a developmental toxicity study, female rabbits were administered of FLUCELVAX (trivalent formulation) by intramuscular injection 1, 3, and 5 weeks prior to mating, and on gestation days 7 and 20. The dose was 0.5 mL on each occasion (a single human dose is 0.5 mL). No vaccine-related fetal malformations or variations and no adverse effects on pre-weaning development were observed in the study.

## 8.2 Lactation

#### Risk Summary

It is not known whether FLUCELVAX QUADRIVALENT is excreted in human milk. Data are not available to assess the effects of FLUCELVAX QUADRIVALENT on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FLUCELVAX QUADRIVALENT and any potential adverse effects on the breastfed child from FLUCELVAX QUADRIVALENT or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine or the effects on milk production.

## 8.4 Pediatric Use

Safety and effectiveness have not been established in children less than 4 years of age.

## 8.5 Geriatric Use

Of the total number of subjects who received one dose of FLUCELVAX QUADRIVALENT in clinical studies and included in the safety population (2493), 26.47% (660) were 65 years of age and older and 7.7% (194) were 75 years of age or older.

Antibody responses to FLUCELVAX QUADRIVALENT were lower in the geriatric (adults 65 years and older) population than in younger subjects. [*see Clinical Studies (14.3)*]

## 11 DESCRIPTION

FLUCELVAX QUADRIVALENT (Influenza Vaccine) is a subunit influenza vaccine manufactured using cell derived candidate vaccine viruses (CVV) that are propagated in Madin Darby Canine Kidney (MDCK) cells, a continuous cell line. These cells were adapted to grow freely in suspension in culture medium. The virus is inactivated with  $\beta$ -propiolactone, disrupted by the detergent cetyltrimethylammonium bromide and purified through several process steps. Each of the 4 virus strains is produced and purified separately then pooled to formulate the quadrivalent vaccine.

FLUCELVAX QUADRIVALENT is a sterile, slightly opalescent suspension in phosphate buffered saline. FLUCELVAX QUADRIVALENT is standardized according to United States Public Health Service requirements for the 2019-2020 influenza season and is formulated to



contain a total of 60 micrograms (mcg) hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA of each of the following four influenza strains:

A/Idaho/07/2018 (an A/Brisbane/02/2018 (H1N1)pdm09-like virus)  
A/Indiana/08/2018 (an A/Kansas/14/2017 (H3N2)-like virus)  
B/Iowa/06/2017 (a B/Colorado/06/2017-like virus)  
B/Singapore/INFTT-16-0610/2016 (a B/Phuket/3073/2013-like virus)

Each dose of FLUCELVAX QUADRIVALENT may contain residual amounts of MDCK cell protein ( $\leq 25.2$  mcg), protein other than HA ( $\leq 240$  mcg), MDCK cell DNA ( $\leq 10$  ng), polysorbate 80 ( $\leq 1500$  mcg), cetyltrimethylammonium bromide ( $\leq 18$  mcg), and  $\beta$ -propiolactone ( $<0.5$  mcg), which are used in the manufacturing process.

FLUCELVAX QUADRIVALENT contains no egg protein or antibiotics.

FLUCELVAX QUADRIVALENT 0.5 mL pre-filled syringes contain no preservative.

FLUCELVAX QUADRIVALENT 5 mL multi-dose vials contain thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose from the multi-dose vial contains 25 mcg mercury.

The tip caps and plungers of the prefilled syringes and the multi-dose vial stopper are not made with natural rubber latex.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance and analysis of influenza virus isolates permits identification of yearly antigenic variants. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of hemagglutination inhibition (HI) antibody titers induced by vaccination with inactivated influenza virus vaccine have not been correlated with protection from influenza illness. In some studies, HI antibody titers of  $\geq 1:40$  have been associated with protection from influenza illness in up to 50% of subjects.<sup>2,3</sup>

Antibody against one influenza virus type or subtype confers little or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual change of one or more strains in each year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the hemagglutinin of influenza virus strains representing the influenza viruses likely to circulate in the United States in the upcoming winter.

**Annual influenza vaccination is recommended by the Advisory Committee on Immunization Practices because immunity declines during the year after vaccination,**

and because circulating strains of influenza virus change from year to year.<sup>4</sup>

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLUCELVAX QUADRIVALENT has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals.

FLUCELVAX (trivalent formulation) administered to female rabbits had no effect on fertility [see Use in Specific Population (8.1)]

### 14 CLINICAL STUDIES

#### 14.1 Efficacy against Culture-Confirmed Influenza

The efficacy experience with FLUCELVAX is relevant to FLUCELVAX QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions.

A multinational (US, Finland, and Poland), randomized, observer-blind, placebo-controlled trial was performed to assess clinical efficacy and safety of FLUCELVAX during the 2007-2008 influenza season in adults aged 18 through 49 years. A total of 11,404 subjects were enrolled to receive FLUCELVAX (N=3828), AGRIFLU (N=3676) or placebo (N=3900) in a 1:1:1 ratio. Among the overall study population enrolled, the mean age was 33 years, 55% were female, 84% were Caucasian, 7% were Black, 7% were Hispanic, and 2% were of other ethnic origin.

FLUCELVAX efficacy was assessed by the prevention of culture-confirmed symptomatic influenza illness caused by viruses antigenically matched to those in the vaccine and prevention of influenza illness caused by all influenza viruses compared to placebo. Influenza cases were identified by active and passive surveillance of influenza-like illness (ILI). ILI was defined as a fever (oral temperature  $\geq 100.0^{\circ}\text{F}$  /  $38^{\circ}\text{C}$ ) and cough or sore throat. Nose and throat swab samples were collected for analysis within 120 hours of onset of an influenza-like illness in the period from 21 days to 6 months after vaccination. Overall vaccine efficacy against all influenza viral subtypes and vaccine efficacy against individual influenza viral subtypes were calculated (Tables 5 and 6, respectively).

Table 5: Vaccine Efficacy against Culture-Confirmed Influenza

	Number of subjects per protocol	Number of subjects with influenza	Attack Rate (%)	Vaccine Efficacy (VE) <sup>1,2</sup>	
				%	Lower Limit of One-Sided 97.5% CI of VE <sup>2,3</sup>
Antigenically Matched Strains					
FLUCELVAX	3776	7	0.19	83.8	61.0
Placebo	3843	44	1.14	--	--
All Culture-Confirmed Influenza					
FLUCELVAX	3776	42	1.11	69.5	55.0
Placebo	3843	140	3.64	--	--

<sup>1</sup>Efficacy against influenza was evaluated over a 9-month period in 2007/2008

<sup>2</sup>Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy (VE) of FLUCELVAX relative to placebo based on the Sidak-corrected score confidence intervals for the relative risk. Vaccine Efficacy = (1 - Relative Risk) x 100 %

<sup>3</sup>VE success criterion: the lower limit of the one-sided 97.5% CI for the estimate of the VE relative to placebo is  $>40\%$

Study: NCT00630331

**Table 6: Efficacy of FLUCELVAX against Culture-Confirmed Influenza by Influenza Viral Subtype**

	FLUCELVAX (N=3776)		Placebo (N=3843)		Vaccine Efficacy (VE) <sup>2</sup>	
	Attack Rate (%)	Number of Subjects with Influenza	Attack Rate (%)	Number of Subjects with Influenza	%	Lower Limit of One-Sided 97.5% CI of VE <sup>1,2</sup>
Antigenically Matched Strains						
A/H3N2 <sup>3</sup>	0.05	2	0	0	--	--
A/H1N1	0.13	5	1.12	43	88.2	67.4
B <sup>3</sup>	0	0	0.03	1	--	--
All Culture-Confirmed Influenza						
A/H3N2	0.16	6	0.65	25	75.6	35.1
A/H1N1	0.16	6	1.48	57	89.3	73.0
B	0.79	30	1.59	61	49.9	18.2

<sup>1</sup>No VE success criterion was prespecified in the protocol for each individual influenza virus subtype.

<sup>2</sup> Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy (VE) of FLUCELVAX relative to placebo based on the Sidak-corrected score confidence intervals for the relative risk. Vaccine Efficacy = (1 - Relative Risk) x 100 %;

<sup>3</sup> There were too few cases of influenza due to vaccine-matched influenza A/H3N2 or B to adequately assess vaccine efficacy.

Study: NCT00630331

There are no data demonstrating prevention of influenza disease after vaccination with FLUCELVAX in the pediatric age group.

#### **14.2 Immunogenicity of FLUCELVAX QUADRIVALENT in Adults 18 years of age and above**

Immunogenicity of FLUCELVAX QUADRIVALENT was evaluated in adults 18 years of age and older in a randomized, double-blind, controlled study conducted in the US (Study 1). In this study, subjects received FLUCELVAX QUADRIVALENT or one of the two formulations of comparator trivalent influenza vaccine (FLUCELVAX QUADRIVALENT (N=1334), TIV1c, N=677 or TIV2c, N= 669). In the per protocol set, the mean age of subjects who received FLUCELVAX QUADRIVALENT was 57.5 years; 55.1% of subjects were female and 76.1% of subjects were Caucasian, 13% were black and 9% were Hispanics. The immune response to each of the vaccine antigens was assessed, 21 days after vaccination.

The immunogenicity endpoints were geometric mean antibody titers (GMTs) of hemagglutination inhibition (HI) antibodies response and percentage of subjects who achieved seroconversions, defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or a pre-vaccination HI titer >1:10 and at least 4-fold increase in serum HI antibody titer.

FLUCELVAX QUADRIVALENT was noninferior to TIVc. Noninferiority was established for all 4 influenza strains included in the QIVc, as assessed by ratios of GMTs and the

differences in the percentages of subjects achieving seroconversion at 3 weeks following vaccination. The antibody response to influenza B strains contained in FLUCELVAX QUADRIVALENT was superior to the antibody response after vaccination with TIVc containing an influenza B strain from the alternate lineage. There was no evidence that the addition of the second influenza B strain resulted in immune interference to other strains included in the vaccine. (See Table 7)

**Table 7: Noninferiority of FLUCELVAX QUADRIVALENT relative to TIVc in adults 18 Years of Age and Above– Per Protocol Analysis Set [Study 1]**

		<b>FLUCELVAX QUADRIVALENT T N = 1250</b>	<b>TIV1c/TIV2c<sup>1</sup> N = 635/N =639</b>	<b>Vaccine Group Ratio (95% CI)</b>	<b>Vaccine Group Difference (95% CI)</b>
A/H1N1	GMT (95% CI)	302.8 (281.8-325.5)	298.9 (270.3-330.5)	1.0 (0.9-1.1)	-
	Seroconversion Rate <sup>2</sup> (95% CI)	49.2% (46.4-52.0)	48.7% (44.7-52.6)	-	-0.5% (-5.3-4.2)
A/H3N2	GMT (95% CI)	372.3 (349.2-396.9)	378.4 (345.1-414.8)	1.0 (0.9-1.1)	-
	Seroconversion Rate <sup>2</sup> (95% CI)	38.3% (35.6-41.1)	35.6% (31.9-39.5)	-	-2.7% (-7.2-1.9)
B1	GMT (95% CI)	133.2 (125.3-141.7)	115.6 (106.4-125.6)	0.9 (0.8-1.0)	-
	Seroconversion Rate <sup>2</sup> (95% CI)	36.6% (33.9-39.3)	34.8% (31.1-38.7)	-	-1.8% (-6.2-2.8)
B2	GMT (95% CI)	177.2 (167.6-187.5)	164.0 (151.4-177.7)	0.9 (0.9-1.0)	-
	Seroconversion Rate <sup>2</sup> (95% CI)	39.8% (37.0-42.5)	35.4% (31.7-39.2)	-	-4.4% (-8.9-0.2)

Abbreviations: HI = hemagglutination inhibition. PPS = per protocol set. GMT = geometric mean titer. CI = confidence interval.

<sup>1</sup>Per protocol set: All subjects in Full Analysis Set, immunogenicity population, who has correctly received the assigned vaccine, have no major protocol deviations leading to exclusion as defined prior to unblinding/ analysis and are not excluded due to other reasons defined prior to unblinding or analysis.

<sup>2</sup>The comparator vaccine for noninferiority comparisons for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 it is TIV2c.

<sup>3</sup> Seroconversion rate = percentage of subjects with either a pre-vaccination HI titer < 1:10 and post-vaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a minimum 4-fold increase in post-vaccination HI antibody titer

Study 1: NCT01992094

#### 14.3 Immunogenicity in Children and Adolescents 4 through 17 years of age

Immunogenicity of FLUCELVAX QUADRIVALENT was evaluated in children 4 through 17 years of age in a randomized, double-blind, controlled study conducted in the US (Study

2). (See section 6.1) In this study, 1159 subjects received FLUCELVAX QUADRIVALENT. In the per protocol set, the mean age of subjects who received FLUCELVAX QUADRIVALENT was 9.8 years; 47% of subjects were female and 54% of subjects were Caucasian, 22% were black and 19% were Hispanics. The immune response to each of the vaccine antigens was assessed, 21 days after vaccination.

The immunogenicity endpoints were the percentage of subjects who achieved seroconversion, defined as a pre-vaccination hemagglutination inhibition (HI) titer of <1:10 with a post-vaccination HI titer  $\geq$ 1:40 or at least a 4-fold increase in serum HI titer; and percentage of subjects with a post-vaccination HI titer  $\geq$ 1:40.

In subjects receiving FLUCELVAX QUADRIVALENT, for all four influenza strains, the 95% LBCI seroconversion rates were  $\geq$ 40% and the percentage of subjects who achieved HI titer  $\geq$ 1:40 post vaccination were  $\geq$ 70% (95% LBCI). (See Table 8)

**Table 8: The Percentage of Children and Adolescents 4 through 17 years of Age with Seroconversion<sup>1</sup> and HI Titers  $\geq$  1:40 post vaccination with FLUCELVAX QUADRIVALENT– Per-Protocol Analysis Set<sup>2</sup> [Study 2]**

		<b>FLUCELVAX QUADRIVALENT</b>
		<b>N = 1014</b>
<b>A/H1N1</b>	<b>Seroconversion Rate<sup>1</sup> (95% CI)</b>	<b>72% (69-75)</b>
	<b>HI titer<math>\geq</math>1:40</b>	<b>99% (98-100)</b>
		<b>N = 1013</b>
<b>A/H3N2</b>	<b>Seroconversion Rate<sup>1</sup> (95% CI)</b>	<b>47% (44-50)</b>
	<b>HI titer<math>\geq</math>1:40</b>	<b>100% (99-100)</b>
		<b>N = 1013</b>
<b>B1</b>	<b>Seroconversion Rate<sup>1</sup> (95% CI)</b>	<b>66% (63-69)</b>
	<b>HI titer<math>\geq</math>1:40</b>	<b>92% (91-94)</b>
		<b>N = 1009</b>
<b>B2</b>	<b>Seroconversion Rate<sup>1</sup> (95% CI)</b>	<b>73% (70-76)</b>
	<b>HI titer<math>\geq</math>1:40</b>	<b>91% (89-93)</b>

Abbreviations: HI = hemagglutinin inhibition. CI = confidence interval.

Analyses are performed on data for day 22 for previously vaccinated subjects and day 50 for not previously vaccinated subjects.

<sup>1</sup> Seroconversion rate = percentage of subjects with either a pre-vaccination HI titer < 1:10 and post-vaccination HI titer  $\geq$  1:40 or with a pre-vaccination HI titer  $\geq$  1:10 and a minimum 4-fold increase in post-vaccination HI titer. Immunogenicity success criteria were met if the lower limit of the 95% confidence interval (CI) of the percentage of subjects with HI titer

≥1:40 is ≥70%; and the lower limit of the 95% CI of the percentage of subjects with seroconversion is ≥40%.

<sup>2</sup>Per protocol set: All subjects in Full Analysis Set, immunogenicity population, who has correctly received the assigned vaccine, have no major protocol deviations leading to exclusion as defined prior to unblinding/ analysis and are not excluded due to other reasons defined prior to unblinding or analysis.

Study 2: NCT 01992107

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4. Centers for Disease Control and Prevention. Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011; 60(33): 1128-1132.

## 16 HOW SUPPLIED / STORAGE AND HANDLING

FLUCELVAX QUADRIVALENT product presentations are listed in Table 9 below:

Table 9: Flucelvax Product Presentations

Presentation	Carton NDC Number	Components
Pre-filled Syringe	70461-319-03	0.5 mL single dose pre-filled syringe, package of 10 syringes per carton [NDC 70461-319-04]
Multi-dose Vial	70461-419-10	5 mL multi-dose vial, individually packaged in a carton [NDC 70461-419-11]

Store this product refrigerated at 2°C to 8°C (36°F to 46°F). Between uses, return the multi-dose vial to the recommended storage conditions. Do not freeze. Protect from light. Do not use after the expiration date.

## 17 PATIENT COUNSELING INFORMATION

Inform vaccine recipients of the potential benefits and risks of immunization with FLUCELVAX QUADRIVALENT.

Educate vaccine recipients regarding the potential side effects; clinicians should emphasize that (1) FLUCELVAX QUADRIVALENT contains non-infectious particles and cannot cause influenza and (2) FLUCELVAX QUADRIVALENT is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against other respiratory illnesses.

Instruct vaccine recipients to report adverse reactions to their healthcare provider.

Encourage women who receive FLUCELVAX QUADRIVALENT while pregnant to enroll in the pregnancy registry. Pregnant women can enroll in the pregnancy registry by calling 1-855-358-8966 or sending an email to Seqirus at [us.medicalinformation@seqirus.com](mailto:us.medicalinformation@seqirus.com).

Provide vaccine recipients with the Vaccine Information Statements which are required by the National Childhood Vaccine Injury Act of 1986. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).

**Inform vaccine recipients that annual vaccination is recommended.**

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**1-855-358-8966**



# **EXHIBIT 268**





Stasis ulcer (Black and Hawks, 2009)

5. suffix meaning an "agent for stopping the growth of": *bacteriostat*, *mycostat*, *fungistat*.

state /stāt/ [L., *status*, condition], the circumstances or qualities that characterize a person, thing, or way of being at a particular time.

state, suffix meaning the "result of a (specified) process": *anastate*, *catastate*, *mesostate*.

state medicine. See **socialized medicine**.

State Nurses Association (SNA), an association of nurses at the state level. The various State Nurses Associations are constituent units of the American Nurses Association.

Statewide Health Coordinating Committee (SHCC), a component of the U.S. national network of Health Systems Agencies.

static /stat'ik/ [Gk., *statikos*, causing to stand], without motion; at rest; in equilibrium. Compare **dynamic**.

static cardiac work, the energy transfer that occurs during the development and maintenance of ventricular pressure immediately before the opening of the aortic and pulmonary valves.

static compliance testing, the difference between maximum and minimum compliance of the middle ear, measured with air pressure.

static equilibrium, the ability of an individual to adjust to displacements of his or her center of gravity while maintaining a constant base of support.

static imaging, 1. a diagnostic procedure for visualizing an internal organ or body compartment. A radioactive substance is administered to a patient, and an image or set of images is made of the fixed or slowly changing distribution of the radioactivity. 2. any diagnostic image that is fixed or frozen in time.

static labyrinth, the vestibule of the inner ear. It contains two communicating chambers, the saccule and the utricle, and elicits tonic reflexes on postural muscles in response to changes in head and body positions.

static pressure [Gk., *statikos*, causing to stand; L., *premere*, to press], a condition of equalized blood pressure throughout the body when the heartbeat is stopped. A nonmoving fluid exerts a uniform pressure in all directions.

static progressive splints, a system of inelastic components that does not allow the person to move the extremity. It increases range of motion by applying a sustained stretch on the joint.

static reflex [Gk., *statikos*, causing to stand; L., *reflectere*, to bend back], a reflex that helps one maintain normal posture and muscle tone when the body is at rest.

static retinoscopy, a type of retinoscopy in which the patient fixes the gaze on an unmoving target at a long distance to relax accommodation.

static scoliosis [Gk., *statikos*, causing to stand, *skoliosis*, curvature], a form of scoliosis resulting from a difference in the length of the legs.

static symptom. See **passive symptom**.

static tremor, irregular involuntary muscle contractions that occur when a patient makes an effort to hold the trunk or limbs in certain positions.

statin. See **HMG-CoA reductase inhibitor**.

station /stā'shan/ [L., *stare*, to stand], the level of the biparietal plane of the fetal head relative to the level of the ischial spines of the maternal pelvis. An imaginary plane at the level of the spines is designated "zero station." Higher and lower stations are numbered at intervals of 1 cm and labeled as minus above and plus below. For example, "station minus three" is 3 cm above the spines, and "station plus two" is 2 cm below the spines. In breech presentation, the bitrochanteric diameter of the breech is used to determine station. See also **dilation**, **effacement**, **labor**.

stationary lingual arch, an orthodontic arch wire that is designed to fit the lingual surface of the teeth and is soldered to the associated anchor bands.

statistic /stetis'tik/ [L., *status*, condition], a number that describes a property of a set of data or other numbers.

statistical model of patient evaluation, a system based on gross quantitative measurements of similar cases used to determine payment for services.

Statistical Package for the Social Sciences. See **SPSS**.

statistical significance [L., *status*, condition, *significare*, to signify], an interpretation of statistical data that indicates that an occurrence was probably the result of a causative factor and not simply a chance result. Statistical significance at the 1% level indicates a 1 in 100 probability that a result can be ascribed to chance.

statistics /stetis'tiks/, a mathematic science concerned with measuring, classifying, and analyzing objective information.

statotonic reflex. See **attitudinal reflex**.

status /stā'tas, stā'tas/ [L., condition], 1. a specified state or condition, such as emotional status. 2. an unremitting state or condition, such as status asthmaticus.

status asthmaticus, an acute, severe, and prolonged asthma attack. It is caused by critically diminished airway diameter resulting from ongoing bronchospasm, edema, and mucous plugging. Hypoxia, cyanosis, and unconsciousness may follow, and the attack may be fatal. Treatment includes supplemental oxygen given to correct hypoxemia, bronchodilators given intravenously or by aerosol inhalation, corticosteroids, mechanical ventilation, sedation, frequent therapy, and emotional support. See also **allergic asthma**, **asthma**.

status dysraphicus. See **dysraphia**.

status epilepticus, a medical emergency characterized by continuous seizures lasting more than 30 minutes without interruption. Status epilepticus can be precipitated by the sudden withdrawal of anticonvulsant drugs, inadequate body levels of glucose, a brain tumor, a head injury, a high fever, or poisoning. Therapy includes IV administration of anticonvulsant drugs, nutrients, and electrolytes. An adequate airway is usually maintained with a nasopharyngeal or endotracheal tube.

status lacunaris. See **lacunar state**.

status marmoratus, the presence in full-term infants of basal nucleus lesions resulting from acute total asphyxia.

[46]



## ELSEVIER

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# **EXHIBIT 269**

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## Statistical Significance

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### Introduction

In research, statistical significance is a measure of the probability of the null hypothesis being true compared to the acceptable level of uncertainty regarding the true answer. If we break apart a study design, we can better understand statistical significance.[1][2][3][4][5][6][7]

When creating a study, the researcher has to start with a hypothesis, that is they must have some idea of what they think the outcome may be. We will use the example of a new medication to lower blood pressure. The researcher hypothesizes that the new medication lowers systolic blood pressure by at least 10 mmHg compared to not taking the new medication. The hypothesis can be then stated, "Taking the new medication will lower systolic blood pressure by at least 10 mmHg compared to not taking the medication." In science, researchers can never prove any statement as there are infinite alternatives as to why the outcome may have occurred. They can only try to disprove a specific hypothesis. The researcher must then formulate a question they can disprove while coming to their conclusion that the new medication lowers systolic blood pressure. The hypothesis, to be disproven, is the null hypothesis and typically the inverse statement of the hypothesis. Thus, the null hypothesis for our researcher would be "Taking the new medication will not lower systolic blood pressure by at least 10 mmHg compared to not taking the new medication." The researcher now has the null hypothesis for the research and must next specify the significance level or level of acceptable uncertainty.

Even when disproving a hypothesis the researcher will not be 100% certain of the outcome. The researcher must then settle for some level of confidence or the significance level for which they do want to be correct. The significance level is given the Greek letter alpha and specified as the probability the researcher is willing to be incorrect. Our researcher wants to be correct about their outcome 95% of the time, or the researcher is willing to be incorrect 5% of the time. Probabilities are stated as decimals with 1.0 being completely positive (100%) and 0 being completely negative (0%). Thus, the researcher who wants to be 95% sure about the outcome of their study is willing to be wrong 5% of the time about the study result. The alpha is the decimal expression of how much they are willing to be wrong. For the current example, the alpha is 0.05. We now have the level of uncertainty the researcher is willing to accept (alpha or significance level) of 0.05 or 5% chance they are not correct about the outcome of the study.

Now the researcher can perform their research. In the example, the researcher would give some individuals the new medication and other individuals, no medication. The researcher then looks to see how the blood pressure changes after receiving the new medication and performs a statistical analysis of the results to obtain a p-value (probability value). There are numerous different tests used in research which can provide a p-value. It is imperative to use the correct statistical analysis tool when calculating the p-value. If the researchers use the wrong test, the p-



value will not be accurate, and this result can mislead the researcher. The p-value is best described as the probability that the null hypothesis is true given the researcher's current set of data. In our example, the researcher found blood pressures did tend to decrease after taking the new medication. The researcher then used the help of their statistician to perform the correct analysis and arrives at a p-value of 0.02 for the decrease in blood pressure for those taking the new medication versus those not taking the new medication. Our researcher now has the three required pieces of information to look at statistical significance: the null hypothesis, the significance level, and the p-value.

The researcher can finally assess the statistical significance regarding the new medication. A study result is stated to be statistically significant if the p-value of the data analysis is less than the prespecified alpha (significance level). In our example, the p-value is 0.02 which is less than the pre-specified alpha of 0.05, so the researcher concludes there is statistical significance for the study.

What does this mean? The p-value of 0.02 implies that there is a 2% chance of the null hypothesis being correct, true, or explained by the current set of data. Remember the null hypothesis states that there is no significant change in blood pressure if the patient is or is not taking the new medication. Thus in this example, there is only a 2% chance the null hypothesis is correct based on the obtained data. The researcher pre-specified an alpha of 0.05 implying they wanted the chance of the null hypothesis to be less than 5% before rejecting the null hypothesis. As the p-value is 0.02 and less than the alpha of 0.05 the researcher rejects the null hypothesis because there is statistical significance. By rejecting the null hypothesis, the researcher accepts the alternative hypothesis. The researcher rejects the idea that there is no difference in systolic blood pressure with the new medication and accepts the alternative that there is a difference of at least 10 mmHg in systolic blood pressure when taking the new medication.

If the researcher had prespecified an alpha of 0.01, implying they wanted to be 99% sure the new medication lowered the blood pressure by at least 10 mmHg, then the p-value of 0.02 would be greater than the prespecified alpha of 0.01. The researcher would conclude the study did not reach statistical significance as the p-value is equal to or greater than the pre-specified alpha. The research would then not be able to reject the null hypothesis.

## Function

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A study is statistically significant if the p-value is less than the pre-specified alpha. Stated succinctly:

- A p-value less than alpha is a statistically significant result
- A p-value greater to or equal to alpha is not a statistically significant result.

## Issues of Concern

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There are a few issues of concern when looking at statistical significance. These issues include choosing the alpha, statistical analysis method, and clinical significance.

Many current research articles specify an alpha of 0.05 for their significance level. It can not be stated strongly enough that there is nothing special, mathematical, or certain about picking an alpha of 0.05. Historically, the originators concluded that for many applications an alpha of 0.05

or a one in 20 chance of being incorrect was good enough. It is imperative for the researcher to consider what their confidence level should truly be for the research question they are asking. Many times a smaller alpha, say of 0.01, maybe more appropriate.

When creating a study, the alpha, or confidence level, should be specified before any intervention or collection of data. It is easy for a researcher to "see what the data shows" then pick an alpha to give a statistically significant result. Such approaches compromise the data and results as the researcher is more likely to be lax on confidence level selection to obtain a result that looks statistically significant.

A second important issue is selecting the correct statistical analysis method. There are numerous methods for obtaining a p-value. The method chosen depends on the type of data, number of data points, and the question being asked. It is important to consider these questions during the study design so the statistical analysis can be correctly identified before the research. The statistical analysis method can then help determine how to collect the data correctly as well as the number of data points needed. If the wrong statistical method is used, the results may be meaningless as an incorrect p-value would be calculated.

## Clinical Significance

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There is a key distinction in statistical significance versus clinical significance. Statistical significance determines if there is mathematical significance to the analysis of the results. Clinical significance means the difference is important to the patient and the clinician. In our study, the statistical significance would be present as the p-value was less than the pre-specified alpha. The clinical significance would be the 10 mmHg drop in systolic blood pressure.[6]

Two studies can have a similar statistical significance but vastly differ in clinical significance. Let us use a hypothetical example of two new chemotherapy agents for treating cancer. Drug A was found to increase survival by at least ten years with a p-value of 0.01 and alpha for the study of 0.05. Thus, this study has statistical significance (p-value less than alpha) and clinical significance (increased survival by ten years). A second chemotherapy agent, Drug B, is found to increase the survival by at least 10 minutes with a p-value of 0.01 and alpha for the study of 0.05. The study for Drug B also found statistical significance (p-value less than alpha) but no clinical significance (a 10-minute increase in life expectancy is not clinically significant). In a separate study, those taking Drug A lived on average eight years after starting the medication versus living for only two more years on average for those not taking Drug A with a p-value of 0.08 and alpha for this second study of Drug A of 0.05. In this second study of Drug A, there is no statistical significance (p-value greater to or equal alpha).

## Other Issues

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Even when a result is statistically significant, it may not be correct. A researcher may thoughtfully design a study with a confidence level of 95% (thus the alpha would be 0.05) and obtain a p-value of 0.04. As the p-value of 0.04 is less than the alpha, the study would be considered to have statistical significance. Based on the alpha of 0.05, the researcher is only 95% sure they are correct in their conclusion. There is thus a 5% chance that although the results are statistically significant the conclusion is nonetheless incorrect.

## Enhancing Healthcare Team Outcomes

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Each member of the health care team needs at least a basic understanding of statistical significance as research throughout all realms, from nursing to surgeons, pharmacists to social workers and all members in between have copious literature with conclusions based on statistical significance. If team members do not have a cohesive and congruent understanding of statistical significance and its implications for research studies and findings then various members may draw opposing conclusions from the same research.

## Questions

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To access free multiple choice questions on this topic, [click here](#).

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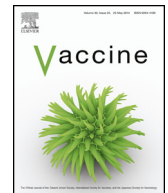
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# **EXHIBIT 270**



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## Vaccine

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## Vaccine hesitancy: Definition, scope and determinants

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## ABSTRACT

The SAGE Working Group on Vaccine Hesitancy concluded that vaccine hesitancy refers to delay in acceptance or refusal of vaccination despite availability of vaccination services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccines. It is influenced by factors such as complacency, convenience and confidence. The Working Group retained the term 'vaccine' rather than 'vaccination' hesitancy, although the latter more correctly implies the broader range of immunization concerns, as vaccine hesitancy is the more commonly used term. While high levels of hesitancy lead to low vaccine demand, low levels of hesitancy do not necessarily mean high vaccine demand. The Vaccine Hesitancy Determinants Matrix displays the factors influencing the behavioral decision to accept, delay or reject some or all vaccines under three categories: contextual, individual and group, and vaccine/vaccination-specific influences.

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## 1. Background

The first tasks of the SAGE Working Group on Vaccine Hesitancy (WG) [1] established in 2012, was to propose a definition of hesitancy and its scope and to develop a model to categorize factors that influence the behavioral decision to accept a vaccine. The WG accomplished these tasks through discussion of the use of the term and similar terms in the scientific literature, review of models of vaccine hesitancy, review of (a) a commissioned systematic review of determinants of vaccine hesitancy [2], (b) field reports and personal observations from the field by different organizations on hesitancy factors, and (c) a commissioned immunization managers' survey of vaccine hesitancy [3], as well as personal observations and experiences of WG members.

## 2. Terminology

As review of the literature did not reveal an established definition, the WG, in its early meetings, discussed at some length whether 'hesitancy' was the most appropriate word to describe the problem. Concerns were raised that hesitancy has a negative connotation. The most commonly offered alternative in the literature was confidence, a more positive word. While confidence covers a range of issues such as trust in vaccines including concerns about

vaccine safety, and trust in health-care workers delivering the vaccine and in those making the decisions to approval of vaccines for a population, confidence is still narrow in scope covering only one category of factors that affect vaccination acceptance decisions (see Matrix Determinants below). Terms such as vaccine acceptance and uptake were also excluded as neither captured the concept breadth i.e. one might accept a vaccine but delay in accepting it i.e. not accepted according to the vaccine schedule. Hence the WG accepted the term hesitancy and then explored potential factors needed in its definition.

During discussions when the WG presented its report to SAGE in October 2014, the concept of vaccine hesitancy versus vaccination hesitancy was also raised. The former implies that the core issue is vaccine related while the latter covers a much wider range of factors such as immunization services, time and place, fear of needles, lack of concern about vaccine preventable diseases, etc. The WG nevertheless chose to adopt the term vaccine hesitancy but defining it in the broader sense (see Definition), noting that SAGE had used it in the terms of reference for the WG, and that this term has become the one more widely accepted in practice.

## 3. Scope

While acceptance of vaccination is the norm in the majority of populations globally, a smaller number refuse some vaccines but agree to others and some delay vaccination or accept vaccination but are unsure in doing so. Hesitancy is thus set on a continuum between those that accept all vaccines with no doubts, to complete refusal with no doubts, with vaccine hesitant individuals the

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<sup>1</sup> See SAGE Working Group on Vaccine Hesitancy members in Appendix A.

heterogeneous group between these two extremes (Fig. 1). While recognizing that hesitant individuals encompass a wide range of people who differ from the very small percentage who refuse all vaccinations and have no doubts about doing this [4,5], the WG concluded that defining vaccine hesitancy on the continuum was not sufficient as it neither defined the scope nor implied the range of factors that influence hesitancy.

In further elucidating the scope, the WG emphasized that hesitancy is a behavioral phenomenon which is vaccine and context specific and measured against an expectation of reaching a specific vaccination coverage goal, given the immunization services available. Vaccine hesitancy may be present in situations where vaccination uptake is low because of system failures, e.g. stock-outs, limited availability of vaccination services (time, place, etc.), curtailment of vaccine services in the presence of conflict or natural disaster, but in these situations hesitancy is not the main explanation for the presence of unvaccinated or under-vaccinated members of the population. Assessing whether hesitancy is present in a population and differentiating hesitancy from other reasons why children/adults are unvaccinated or under-vaccinated is essential for the selection of interventions needed to address low vaccine uptake.

#### 4. Vaccine hesitancy versus vaccine demand

The Working Group examined the relationship between vaccine hesitancy and vaccine demand [6]. In the Global Vaccine Action Plan, approved by the World Health Assembly in May 2012, Strategic Objective 2 states that “individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility” [p. 38].

As illustrated in Fig. 1, vaccine hesitancy occurs on the continuum between high vaccine demand and complete vaccine refusal, i.e. no demand for available and offered vaccines. However, demand and hesitancy are not completely congruent. An individual or community may fully accept vaccination without hesitancy but may not demand vaccination or a specific vaccine. The following examples illustrate demand aspects that go beyond hesitancy. In Uttar Pradesh, India, the community demanded, through the courts, public access to Japanese encephalitis vaccine to curb annual disease outbreaks associated with high morbidity and mortality among their children [7]. In Calgary, Canada, in-school access to Human Papilloma Virus vaccine was prohibited in Catholic schools in 2008, but citizens’ demand successfully overturned this ban in 2013 and

supported in-school access to HPV vaccination as had previously been available only in non-Catholic public schools [8].

Because hesitancy undermines demand, to achieve the vaccine demand goal, as defined in the Global Vaccine Action Plan, countries will need to take action to counteract hesitancy. When rates of hesitancy are high, levels of demand are low, but low rates of hesitancy do not necessarily mean that demand will be high. To achieve high individual and community vaccine demand, context, community and vaccine specific strategies beyond those aimed at addressing hesitancy need to be developed.

#### 5. Vaccine hesitancy models

Acceptance of vaccination is an outcome behavior resulting from a complex decision-making process that can be potentially influenced by a wide range of factors. In developing the definition, the WG in 2012 reviewed a number of conceptual models for grouping vaccine hesitancy determinants [2,9–11]. In the review, model complexity, global applicability, breadth of factors considered and potential usefulness in informing the development of vaccine hesitancy indicators and survey questions for use at the global and country levels were all considered. The WG also assessed whether the model could facilitate understanding of the concept of vaccine hesitancy for those unfamiliar with the term.

Review of these models confirmed the complexity of vaccine hesitancy and its determinants. The “3 Cs” model, first proposed to the WHO EURO Vaccine Communications Working Group in 2011 [9], highlights three categories; complacency, convenience and confidence (Fig. 2). As this model was viewed as being the most readily understandable, the concepts were incorporated in the definition.

In the “3 Cs” model, *confidence* is defined as trust in (i) the effectiveness and safety of vaccines; (ii) the system that delivers them, including the reliability and competence of the health services and health professionals and (iii) the motivations of policy-makers who decide on the needed vaccines.

Vaccination *complacency* exists where perceived risks of vaccine-preventable diseases are low and vaccination is not deemed a necessary preventive action. Complacency about a particular vaccine or about vaccination in general is influenced by many factors, including other life/health responsibilities that may

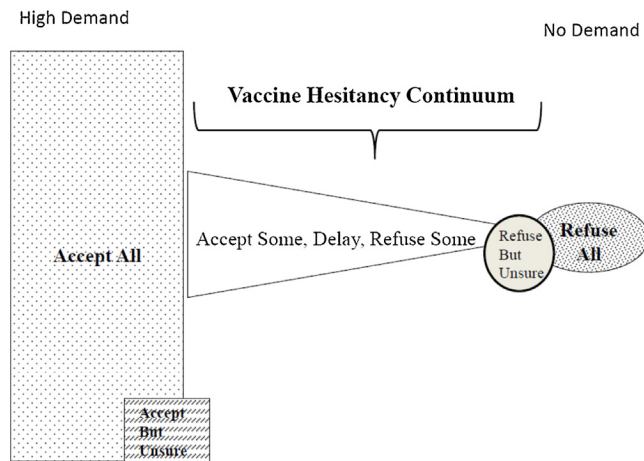


Fig. 1. The continuum of vaccine hesitancy between full acceptance and outright refusal of all vaccines.

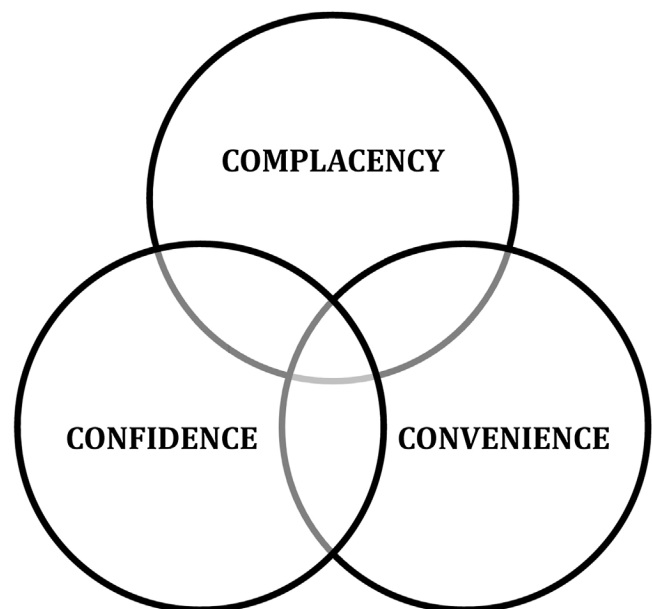


Fig. 2. “Three Cs” model of vaccine hesitancy.

**Table 1**

Working Group on Vaccine Hesitancy Determinants Matrix.

Contextual influences Influences arising due to historic, socio-cultural, environmental, health system/institutional, economic or political factors	a. Communication and media environment b. Influential leaders, immunization programme gatekeepers and anti- or pro-vaccination lobbies c. Historical influences d. Religion/culture/gender/socio-economic e. Politics/policies f. Geographic barriers g. Perception of the pharmaceutical industry
Individual and group influences Influences arising from personal perception of the vaccine or influences of the social/peer environment	a. Personal, family and/or community members' experience with vaccination, including pain b. Beliefs, attitudes about health and prevention c. Knowledge/awareness d. Health system and providers – trust and personal experience e. Risk/benefit (perceived, heuristic) f. Immunization as a social norm vs. not needed/harmful a. Risk/benefit (epidemiological and scientific evidence)
Vaccine/vaccination – specific issues Directly related to vaccine or vaccination	b. Introduction of a new vaccine or new formulation or a new recommendation for an existing vaccine c. Mode of administration d. Design of vaccination programme/Mode of delivery (e.g., routine programme or mass vaccination campaign) e. Reliability and/or source of supply of vaccine and/or vaccination equipment f. Vaccination schedule g. Costs h. The strength of the recommendation and/or knowledge base and/or attitude of healthcare professionals

be seen to be more important at that point in time. Immunization programme success may, paradoxically, result in complacency and ultimately, hesitancy, as individuals weigh risks of vaccination with a particular vaccine against risks of the disease the vaccine prevents that disease is no longer common. Self-efficacy (the self-perceived or real ability of an individual to take action to be vaccinated) also influences the degree to which complacency determines hesitancy.

Vaccination *convenience* is a significant factor when physical availability, affordability and willingness-to-pay, geographical accessibility, ability to understand (language and health literacy) and appeal of immunization services affect uptake. The quality of the service (real and/or perceived) and the degree to which vaccination services are delivered at a time and place and in a cultural context that is convenient and comfortable also affect the decision to be vaccinated and could lead to vaccine hesitancy.

## 6. Vaccine hesitancy determinants matrix

After review of models and much discussion about factors that can influence hesitancy, the WG developed the Vaccine Hesitancy Determinants Matrix with factors grouped in three categories: *contextual, individual and group* and *vaccine/vaccination-specific influences* (Table 1). The Matrix includes determinants identified from research studies, experiences of WG members in the field, and discussions with experts working in the area. Neither the commissioned systematic review of determinants [2], nor the findings from the WG's Immunization Managers Survey on hesitancy [3] uncovered new determinants that had not been included in the Matrix.

Of note, unlike with the social determinants of health, vaccine hesitancy determinants like education and socio-economic status do not influence hesitancy in only one direction. As shown in the commissioned systematic review, higher education may be associated with both lower and higher levels of vaccine acceptance [2]. In contrast, as a social determinant of health, education drives in one direction – more education leads to better health outcomes [12].

## 7. Vaccine hesitancy and communication

The Working Group discussed whether poor communication was a determinant of vaccine hesitancy. The Working Group concluded that communication was a tool not a determinant. While communication is not a specific factor, like confidence, complacency and convenience, when it is poor or inadequate it can negatively influence vaccination uptake and contribute to vaccine

hesitancy. Poor quality services of any type, including poor communication, can undermine acceptance. This can be a problem in any setting. In high income countries with well-resourced vaccination programs, inadequate or poor immunization program communications can increase vaccine hesitancy and outright refusal. For example, in 1999, the reason underlying the decision to minimize thimerosal as a preservative in some vaccines in the USA was poorly communicated. As a consequence, this undermined public confidence in vaccination, leading to vaccine hesitancy and refusal [13]. In low and middle income countries, scarce communication resources limit the capacity to counter negative information about vaccines and achieve community support for vaccination programs. For instance, the Independent Monitoring Board on Polio Eradication noted deep concern about “*the Global Programme's weak grip on the communications and social mobilization that could not just neutralize communities' negativity, but generate more genuine demand. Within the Programme, communications is the poor cousin of vaccine delivery, undeservedly receiving far less focus. Communications expertise is sparse throughout and needs to be strengthened*” [14]. The WHO African Task Force on Immunization is collaborating with UNICEF on the development of a tool to improve vaccination programme communications in the region because these deficiencies, especially during crises, may result in significant vaccine hesitancy.

Thus, regardless of the setting and causes of vaccine hesitancy, poor communication needs to be addressed generally, in addition to developing targeted communication to address hesitancy issues and improve vaccination uptake. In this supplement Goldstein et al. [15] provide a brief introduction to health communication in the context of vaccine hesitancy.

## 8. Definition of vaccine hesitancy

Following its deliberations, the WG decided upon the following definition:

*Vaccine hesitancy refers to delay in acceptance or refusal of vaccination despite availability of vaccination services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccines. It is influenced by factors such as complacency, convenience and confidence.*

## 9. Conclusions

The Working Group concluded that this practical definition of vaccine hesitancy was needed in order to ensure that Immunization Programme Managers, policy makers, clinicians and researchers



would consistently use a standard term to cover the broad range of factors causing low vaccination uptake while excluding those not related to personal/community behavior choices. That low vaccine uptake may not be due to hesitancy must be born in mind when selecting interventions to improve uptake. The Vaccination Determinants Matrix, while not primarily intended as a practical tool, may be helpful for researchers, survey question developers and those developing interventions to address hesitancy to approach the problem more broadly than as simply an issue of confidence.

#### Conflict of interest statement

The LSHTM research group “Project to monitor public confidence in Immunization Programs” has received research funding from Novartis as well as funding from GSK to host a meeting on vaccine confidence. Heidi Larson has done consulting on vaccine confidence with GSK.

None of the other authors had any potential conflict of interest.

Some of the authors are World Health Organization staff members. The opinions expressed in this article are those of the authors and do not necessarily represent the decisions, official policy or opinions of the World Health Organization.

#### Appendix. SAGE Working Group on Vaccine Hesitancy

Juhani Eskola, National Institute for Health and Welfare, Finland (Chair of Working Group since April 2014); Xiaofeng Liang, Chinese Center for Disease Control, China (Member of SAGE until 2014, Chair of Working Group from March 2012 to April 2014); Mohuya Chaudhuri, Independent Journalist and Documentary Filmmaker, India; Eve Dubé, Institut National de Santé Publique du Québec, Canada; Bruce Gellin, Department of Health and Human Services, U.S.A.; Susan Goldstein, Soul City: Institute for Health and Development Communication, South Africa; Heidi Larson, London School of Hygiene and Tropical Medicine, U.K.; Noni MacDonald, Dalhousie University, Canada; Mahamane Laouali Manzo, Ministry of Health, Niger; Arthur Reingold, University of California at Berkeley, U.S.A.; Kinzang Tshering, Jigme Dorji Wangchuck National Referral Hospital, Bhutan; Yuqing Zhou, Chinese Center for Disease Control, China with the WHO/UNICEF Secretariat; Robb Butler, World Health Organization, Denmark; Philippe Duclos, World Health Organization, Switzerland; Sherine Guirguis, UNICEF, U.S.A.; Ben

Hickler, UNICEF, U.S.A.; Melanie Schuster, World Health Organization, Switzerland.

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# **EXHIBIT 271**



# The rise (and fall?) of parental vaccine hesitancy

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Parental vaccine hesitancy is a growing problem affecting the health of children and the larger population. This article describes the evolution of the vaccine hesitancy movement and the individual, vaccine-specific and societal factors contributing to this phenomenon. In addition, potential strategies to mitigate the rising tide of parent vaccine reluctance and refusal are discussed.

## Introduction

A resurgence of outbreaks of vaccine-preventable diseases (VPDs), including measles and pertussis,<sup>1-5</sup> has prompted renewed attention on how vaccine hesitancy can lead to the spread of infection and negatively impact public health. However, vaccine hesitancy is not a new phenomenon. Concern and controversy over the relative benefit vs. potential harm of vaccines have been long debated by the public, ever since the 18th century when Jenner's use of the cowpox virus to provide immunity against smallpox first demonstrated the principle of vaccination.<sup>6,7</sup> Over time, due to changes in the prevalence of VPDs, the ability to rapidly disseminate information (including supposed vaccine "controversies") via traditional media and the internet, and the increasing number of vaccines now available or under development, there has been an evolution in the public's understanding of vaccines and the predominant concerns that fuel vaccine hesitancy today.

In this article, we examine the increasing trend of parental vaccine hesitancy over time, the factors engendering vaccine doubt among "vaccine-hesitant parents" (VHPs), and potential strategies to address vaccine hesitancy when it arises. We focus specifically on vaccines recommended for children and adolescents, which require parental awareness and acceptance for vaccine administration.

## Trends in Vaccine Hesitancy over Time

Although coverage levels for most childhood vaccines remain high in the United States,<sup>8,9</sup> numerous studies have documented that vaccine-related confidence has been decreasing among US parents over the past several years. In a national study of parents performed in 2000, 19% indicated they had "concerns about vaccines" whereas in a subsequent survey performed in 2009 this

number had risen to 50%.<sup>10,11</sup> Concurrent with the rise in parental vaccine hesitancy is the steady increase in non-medical vaccine exemptions that has occurred over the last several years.<sup>12</sup> In a 2010 National survey of physicians, 89% of respondents reported at least one vaccine refusal by a parent each month.<sup>13</sup>

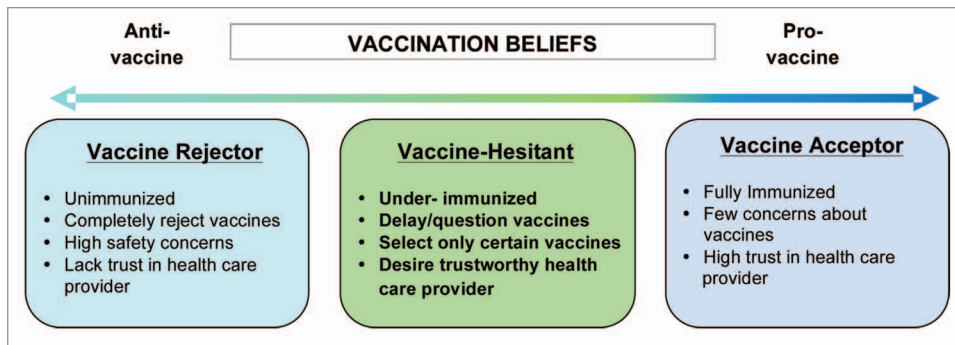
Vaccine hesitancy can take several forms. At its most severe, parents refuse all recommended vaccines. However, this viewpoint is relatively rare, adopted by only 1–2% of parents nationally.<sup>11,14–16</sup> Instead, delay or refusal of one or more specific vaccines is much more common. For example, in a national study performed by Gust et al. in 2003, 28% of parents reported vaccine hesitancy, of which approximately two-thirds delayed or refused only certain vaccines.<sup>16</sup> In a study by Freed et al. performed in 2009, 11.5% of parents nationally had refused at least one vaccine for their child, occurring most commonly with human papillomavirus and varicella vaccine, with 56% and 32% of vaccine-refusing parents reporting refusal of these specific vaccines, respectively. In a 2010 study by Dempsey et al., H1N1 and seasonal influenza vaccine were the most commonly refused vaccines, reported by 86% and 76% of vaccine-hesitant parents, respectively. Another form of vaccine hesitancy is when parents elect to have all vaccines provided to their children on delayed schedule. This alternative schedule is less common than refusing or delaying only specific vaccines, but more common than complete vaccine refusal.

## Public Health Impact of Vaccine Hesitancy

With the rise of vaccine hesitancy, increasing numbers of children are being put on "alternative" vaccine schedules that differ from the recommended immunization schedule. This results in unnecessarily increased periods of "risk exposure" for contracting a VPD.<sup>14</sup> Consistent with this, the incidence of several vaccine-preventable diseases has been on the rise. In 2008 alone, the US saw 140 measles cases, more than twice the average number of annual cases from 2000 to 2007.<sup>17</sup> According to the Centers for Disease Control and Prevention (CDC), this increase was not due simply to greater numbers of imported cases but also to greater viral transmission within communities of unvaccinated individuals—99 of 106 US-born cases with known vaccination histories were unvaccinated.<sup>18</sup> Historically significant outbreaks of pertussis, mumps and rubella have also occurred in the US, largely within under- or unvaccinated populations.<sup>1,17–21</sup>

Other countries have witnessed similar outbreaks of vaccine-preventable diseases associated with increasing concerns about vaccine-related safety. Devastating outcomes were seen in Nigeria, for example, where concerns about polio vaccination safety led to

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**Figure 1.** Continuum of parental vaccine acceptance.

a suspension of polio immunization activities in 2003 and 2004, with a resultant rise in cases.<sup>22</sup> VPDs have resurged in countries of all stages of development. Similar to the US, other developed countries in western Europe and Australia have seen measles, mumps, rubella or pertussis outbreaks in recent years.<sup>23-26</sup> After publication of Wakefield's now discredited hypothesis that the MMR vaccine is associated with autism,<sup>27,28</sup> MMR vaccination levels sharply dropped in many European countries and remain below those seen prior to 1998;<sup>29</sup> as a result these countries have seen a rise in cases of measles.<sup>25,30</sup> Outbreaks of rubella and mumps have been documented in communities with low-vaccination rates in the Netherlands.<sup>24,26</sup>

### Defining Vaccine Hesitant Parents

At least one in four parents expresses serious reservations about the recommended childhood vaccine schedule and can thus be broadly categorized as a VHP.<sup>16,31</sup> Yet, vaccine-hesitant parents are actually comprised of a widely heterogeneous group, displaying a variety of attitudes and beliefs toward specific vaccines, vaccine schedule preferences and vaccination intentions and behaviors. Because of this, VHPs may be best understood as falling within a spectrum, ranging from those vehemently opposed to all vaccines to those who demonstrate universal support for vaccines (Fig. 1).

Numerous studies have addressed the heterogeneity of VHPs by attempting to categorize such parents into "subsets" based on their specific beliefs or level of vaccine hesitancy. For example, Gust et al.<sup>32</sup> used data from surveys of parental attitudes and beliefs regarding immunizations to generate 5 categories of VHPs with similar attitudinal subsets. These included "Immunization Advocates," "Go Along to Get Alongs," "Health Advocates," "Fence-sitters" and "Worrieds." In a different framework developed by Leask et al.,<sup>33</sup> both vaccine hesitant and non-hesitant parents were classified into five groups regarding their immunization beliefs. These groups ranged from the "Unquestioning Acceptor" to the "Refuser," with three interim groups describing VHPs: "Cautious Acceptors," "Hesitants," "Late/Selective" vaccinators.

More recently, Opel et al. have developed a questionnaire to classify vaccine-hesitant parents into different "levels" of vaccine hesitancy and validated the predictive capacity of these

categorizations to reflect future vaccination behaviors.<sup>31,34</sup> Such a tool will be extremely helpful for developing interventions so that the content and presentation (e.g., gain- vs. loss-framed messages, personal narratives vs. fact lists) of vaccine-related information provided can match each parent's specific vaccines concerns, knowledge and beliefs, and information preferences. The need for this type of "matching" is supported by a recent study of vaccination barriers among MMR vaccine-hesitant parents. This study demonstrated that

providing information to counteract MMR vaccine-specific concerns had varying degrees of influence on parents in their decision-making for the vaccine depending on their relative "level" of vaccine-hesitancy.<sup>35</sup>

### Factors Affecting Vaccine Hesitancy

Given the diversity observed among VHPs, it can be helpful to use a framework to understand the multiple "levels" of factors that influence vaccine confidence and acceptance (Fig. 2). Understanding how vaccine-specific, individual-level, and "external" (i.e., societal, familial) factors impact vaccine hesitancy will likely be important for developing effective interventions in the future to mitigate this problem. While these factors are presented separately, it is important to acknowledge their interrelatedness. For example, external factors such as media portrayals of vaccine controversies can drive changes individual knowledge and beliefs.

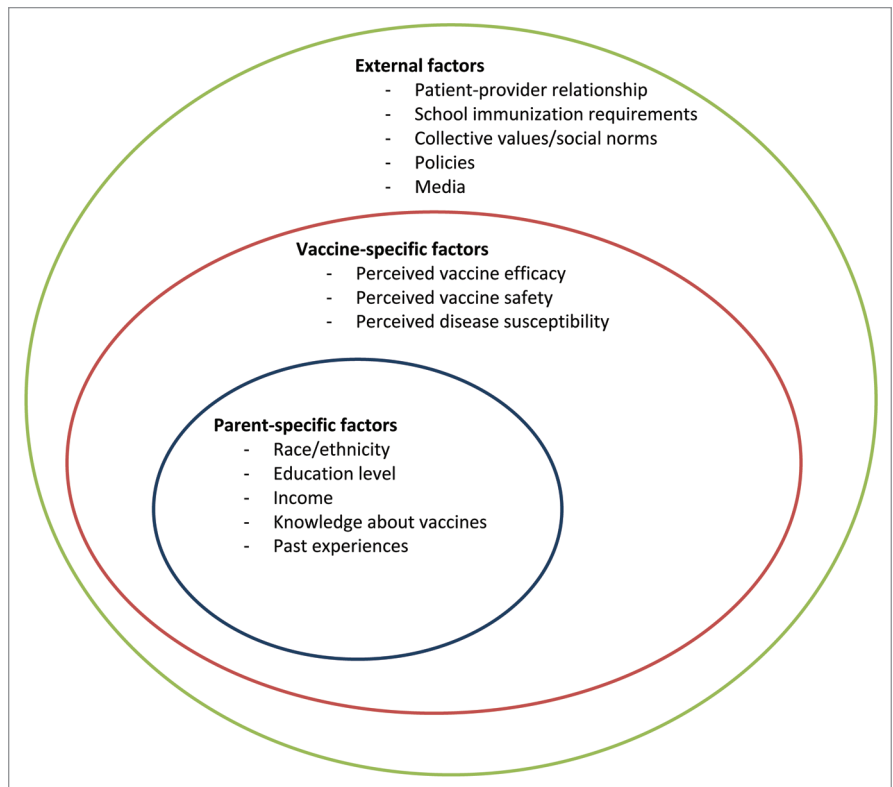
**Vaccine-specific beliefs that impact vaccine hesitancy.** Vaccine-specific factors impact vaccine decision-making by moderating perceptions about the relative risks and benefits to vaccinating vs. not vaccinating. Concerns about the immediate or short-term side effects of vaccines are significant drivers of vaccine delay and/or refusal. In a study of parents of young children aged 6 y or less, common concerns identified by parents included pain during injections and fevers after vaccination.<sup>36</sup> Qualitative studies have also suggested that vaccine-hesitant parents are significantly concerned about the immediate side effects of vaccines. For example, Shui et al.<sup>37</sup> conducted focus groups of African-American mothers and found that a majority expressed reservations about potential adverse reactions from vaccines such as redness, swelling or pain at the injection site. The discomfort associated with vaccinations remains a significant barrier to vaccination, even as children age. Parents of adolescents commonly report that fear of needles and the associated pain are important considerations that influence their intention to vaccinate their children.<sup>38</sup>

Parental concerns about vaccine safety extend beyond the immediate, localized reactions to fear of potential, long-lasting complications, including neurologic conditions. Although the purported association between the measles vaccine and autism has been scientifically disproven,<sup>39,40</sup> some parents continue to

express reservations about the MMR vaccine causing this problem.<sup>36,41-43</sup> The influenza vaccine is another example, where some parents are worried that this vaccine may lead to Guillain-Barre syndrome although numerous studies of current formulations of the influenza vaccine have not been able to validate such an association.<sup>44</sup> Other parents express reservations about vaccine safety in general, emphasizing the potential risks of vaccination over those of the disease, reflecting a well-established human propensity for omission bias (i.e., preferring the consequences of not doing something to the consequences of doing something).<sup>42,45</sup>

Additional concerns about vaccine safety focus on the number and timing of recommended vaccines. Multiple vaccines have been newly introduced and adopted into the recommended childhood vaccination schedule including rotavirus, Tdap, meningococcal and HPV vaccines.<sup>46</sup> With additional new vaccines in the pipeline, the number of recommended vaccines is slated to grow in the future. This has alarmed parents who fear that too many vaccines, especially in a short period of time, could be harmful for their children. Specifically, some parents are concerned about the cumulative pain and discomfort experienced by children who receive multiple shots at once. Others worry about the potential health risks of receiving multiple vaccinations during one clinic visit, wondering whether the body can handle so many different antigens at once. Additionally, parents question whether the immune system may become overloaded by receipt of all the recommended vaccines during early childhood.<sup>36,37</sup> Given these concerns, there is clearly a need for greater dissemination of information about vaccine development and safety monitoring.<sup>47</sup>

Perceptions about vaccine efficacy are an integral factor in the vaccination decision for VHPs and can be broken down into two components: (1) perceived susceptibility to disease and (2) perceived efficacy of vaccine-induced immunity. The overwhelming success of vaccination efforts in drastically reducing the incidence of VPDs over the last century has resulted in diminished exposure to VPDs and associated complications. As a result, parents do not perceive such illnesses to necessarily be significant health threats. For example, the elimination of measles as an infection endemic to the US as of 2000<sup>48</sup> has led parents to question whether there is a continued need for the measles vaccine. With overall high immunization levels in the US, some parents perceive that there is a diminished need for their children also to be vaccinated, assuming they will benefit from herd immunity.<sup>42</sup> Vaccine doubts among VHPs are further fueled by the resulting imbalance between decreasing levels of perceived disease susceptibility and increasing concerns about vaccine safety.



**Figure 2.** Framework for understanding the different types of factors influencing parental vaccine hesitancy.

Among vaccine-hesitant parents, there is significant concern over the relative efficacy of vaccine-induced immunity vs. immunity obtained through the natural course of disease, with some parents preferring their children obtain immunity “naturally” as opposed to via vaccination.<sup>49-51</sup> There are several possible reasons fostering this belief. First, personal experience with a limited form of the disease may have led parents to believe that disease-related risks are low and relatively inconsequential. This is particularly true for the varicella vaccine, as many parents recall having had varicella during childhood and generally lack awareness of the potentially serious complications associated with the disease. Interestingly, some parents also cite a preference for naturally acquired infection as a reason for not giving their children the measles-containing vaccine. In this case, lack of personal experience with the disease may lead parents to underestimate the risk of devastating complications from infection.<sup>37,43</sup> This preference for natural immunity indicates a lack of understanding about vaccination principles, suggesting a potential target area for future educational campaigns.

Finally, uncertainty about vaccines is fueled by ongoing and frequent changes to the childhood vaccine schedule, both by the Advisory Committee on Immunization Practices (ACIP) on a national scale, and by physicians within local practices. For example, immunization delays or changes to vaccine recommendations due to vaccine shortages, as seen during the *Hemophilus influenza* Type b conjugate vaccine shortage from 2007 to 2008,<sup>52</sup> can raise doubts among parents about the importance

of strictly adhering to the recommended vaccine schedule. As a result, physicians may have a more challenging time explaining why vaccines should not be delayed due to parental preference. Furthermore, alterations to vaccine recommendations may confuse parents or raise concerns about what prompted the changes. For example, some parents of adolescents raised doubts about why the influenza vaccine was now being recommended for adolescents when previously it had not been.<sup>38</sup> Thus, it is imperative that physicians and public health professionals inform parents not only about changes to vaccine schedules, but also why these new recommendations are being adopted, so as to provide an opportunity for newly arising concerns to be discussed.

**Individual-level factors.** Individual-level factors such as socioeconomics, race, and education level directly impact each person's concept of the risks and benefits of vaccination vs. the risks and sequelae of a VPD. Socioeconomic factors appear to have conflicting associations with parental immunization acceptance, which could reflect differences in underlying beliefs about vaccines that differ by socioeconomic strata. Parents of lower-income brackets have been shown in some studies to have greater levels of concern about the safety and necessity of vaccines as compared with those of higher income.<sup>31,53-55</sup> For example, in one national survey of parents of young children, those in the lowest income category reported nearly 50% higher levels of agreement that vaccinations are associated with serious side effects and significantly lower levels of agreement that their children are susceptible to VPDs and that vaccines can be protective against VPDs than higher income parents.<sup>54</sup> In fact, when US parents who oppose compulsory vaccination were studied, lower income was the only socio-demographic characteristic independently associated with vaccination opposition.<sup>55</sup> In contrast however, Opel et al. showed that while parents with household incomes >\$75,000 were 2-fold more likely to be unconcerned about serious vaccine-related adverse reactions than those with lower incomes, the opposite effect was found when examining the association between income and attitudes about vaccine safety.<sup>31</sup> Parents in the higher income bracket were more than two times as likely as parents from lower income brackets to be concerned that shots might not be safe. The apparent contradiction could be related to differing perceptions of what "vaccine safety" means among parents from different socioeconomic backgrounds. For example, parents in high-income brackets may relate "vaccine safety" to concerns such as autism or autoimmune disease, but "vaccine-related adverse events" to consequences like fever or soreness. In contrast, parents in lower income brackets might interpret these terms differently. Further study is needed to better understand what terms like "side effects," "safety" and "adverse events" mean to different populations of people so that effective public health messages can be crafted.

Level of parental education has also been implicated as contributing to vaccine hesitancy. Several studies demonstrate that parents with less formal education have greater distrust in the medical community, express more concerns about vaccine safety and have less belief in the necessity and efficacy of vaccines.<sup>31,50,53,54,56</sup> Gust et al.<sup>56</sup> found that parents with less than 12 y of education were more likely to report not having enough

vaccination information, compared with parents with some graduate school education. This, combined with greater distrust in the medical community, may lead these parents to seek out alternative sources of information such as family members, other parents in the community, or the media.<sup>41,42</sup> The increasing prevalence of anti-vaccination messages presented in these outlets likely contributes further propagating parental vaccine hesitancy.<sup>57-59</sup> However, like income, there appears to be a conflicting influence of education on vaccination attitudes. For example, Opel et al. found that parents with higher levels of education were nearly four times as likely to be concerned about the safety of vaccine than those from lower education levels.<sup>31</sup> Similarly, Smith et al. found that refusal of all childhood vaccines was more common among college educated parents than those with lower levels of education.<sup>60</sup>

While some studies have suggested that African-American children have lower immunization coverage levels compared with other race groups,<sup>61-63</sup> more recent data have not shown significant differences in national vaccine coverage levels by racial/ethnic groups, particularly after adjustment for poverty status.<sup>8,9</sup> However, some studies have shown that race/ethnicity is associated with differential levels and types of immunization concerns.<sup>36,39,50,51</sup> For example, in a nationally representative sample of parents of children ≤18 y where parents were categorized by their level of immunization safety concern, very concerned parents were more likely to be black or Hispanic compared with whites.<sup>53</sup> Prislín et al.<sup>50</sup> showed that African-Americans endorsed weaker beliefs in the protective value of vaccines, resulting in decreased vaccine acceptance when compared with Hispanics and white Americans. Interestingly, Freed et al.<sup>43</sup> found in a national survey of parents that Hispanics, despite being more concerned about the serious adverse effects of vaccines, were also more likely than comparator groups to follow their doctors' vaccine recommendations, and less likely to have ever refused a vaccine. This latter finding supports the observation that simply expressing vaccine-related concerns does not directly translate to decreased vaccine administration. Given these concerns, there is clearly a need for greater dissemination of information about vaccine development and safety monitoring.<sup>61,62</sup>

**External factors.** External factors moderate vaccine decision-making by shaping societal norms which, in turn, can impact individuals' perceptions about disease risk and prevention (either positively or negatively). Physicians overwhelmingly remain one of the most important sources of information for parents about their children's health. Numerous studies demonstrate that the strength of recommendations and emphasis placed on immunizations by the provider can influence a parent's confidence in (and thus acceptance of) vaccines.<sup>54</sup> Smith et al.<sup>65</sup> showed that parents who reported that their vaccination decisions were positively influenced by healthcare providers were also more likely to believe that vaccines were safe. However, providers who share vaccine-related concerns or place less importance on vaccines may transmit these beliefs to their patients and families. Salmon et al.<sup>66</sup> compared the vaccination knowledge and practices between primary care providers of fully vaccinated children and those of children who received exemptions from school



immunization requirements. Compared with fully vaccinating providers, those who cared for exempt children had significantly increased concerns about vaccine safety and perceived less benefit from vaccines.<sup>66</sup>

“Quality” of the relationship between parents and the health care provider also appears to be important. Gust et al.<sup>54</sup> found that parents with lower levels of trust in their child’s doctor also had lower confidence in the safety of vaccines.<sup>54</sup> Level of trust is an important distinguishing factor between parents who adamantly oppose vaccines (i.e., “vaccine refusers”) vs. VHPs. “Refusers” generally report greater distrust of healthcare providers and place less emphasis on providers’ recommendations when making healthcare decisions. In contrast, VHPs appear to align more with “vaccine acceptors,” expressing a willingness to listen to providers’ healthcare recommendations.<sup>42,67</sup> Given this, healthcare providers could help restore vaccine confidence among VHPs by promoting healthy lines of communication with and offering multiple avenues for information gathering for patients and families.

Vaccine confidence and immunization decisions are also driven by perceived social norms or collective values. Many parents rely on other parents or family members as sources of vaccine-related information.<sup>58</sup> Specifically, decisions to immunize are mediated in part by perceptions of what other parents in the community are doing.<sup>68-70</sup> Vaccine concerns endorsed by a small but highly vocal subset of VHPs may heighten vaccine hesitancy among other parents in the community, as is supported by studies demonstrating geographic clustering of non-medical exemptions to school-required vaccines.<sup>71</sup> Additionally, media including print, television and the internet, can help inform people about current societal practices, and the increased prevalence of concerns, fears and misinformation about vaccines. Propagation of “fear stories” likely has contributed to the growth of vaccine hesitancy in the US and internationally.<sup>57-59,72</sup> It is important to note, however, that the impact of collective values can be bidirectional - parental decisions to vaccinate their children can be positively influenced by the desire to be a “good parent.”<sup>37</sup>

Finally, public policies such as school mandates and the ease or difficulty with which exemptions to these mandates can be obtained also appear to influence vaccine acceptance. School requirements significantly increase vaccine coverage levels, presumably by swaying some “Fence Sitters” toward vaccinating. As an added benefit, mandates for one vaccine may also result in a “spill-over effect” to improve vaccination levels for other, non-mandated vaccines.<sup>73-75</sup> Closely related to the effectiveness of school mandates is the ease with which exemptions for such mandates can be obtained. Rota et al. demonstrated that at a state level, greater difficulty in obtaining non-medical vaccine exemptions was inversely associated with the proportion of children who had such an exemption filed.<sup>76</sup>

*Strategies to address vaccine hesitancy.* Clearly, parental vaccine hesitancy is a growing problem with a significant public health impact. As described above, challenges to maintaining adequate vaccine coverage include overcoming negative vaccine- and individual-specific attitudes and beliefs amidst a continual barrage of external factors such as vaccine controversies and evolving

vaccination schedules that can also affect vaccination acceptance. While strategies such as enforcing school mandates for immunization, minimizing policies that promote non-medical exemptions, and maintaining public health and financial support for vaccination have a positive impact on vaccination rates, additional, novel strategies are also needed to counteract the growing negativity of parental vaccination attitudes.

*Tailoring information.* One mechanism that shows promise for mitigating the effects of negative vaccine- and individual influences is the use of tailored educational materials. Tailored materials target each individual’s unique experiences, beliefs and attitudes about vaccination, which can result in perceptions that the information provided is more relevant, and thus more trustworthy and influential.<sup>77</sup> Tailored messaging approaches have been shown across diverse populations and health issues to be superior to non-tailored information for improving compliance with recommended health behaviors.<sup>77-83</sup> The few studies have that used this approach with regard to vaccine hesitancy suggest it may be similarly effective. For example, in one study of 80 MMR-vaccine hesitant parents, those who received a website that was tailored to their specific attitudinal barriers about the vaccine were significantly more likely to have positive intentions for their child to receive the MMR vaccine in the coming year than those who received untailored information.<sup>84</sup> Similar results were found in second study that used the same methodology and comparison groups, but targeted mothers with concerns about HPV vaccination.<sup>85</sup> Finally, Gust et al. developed a series of educational brochures that were reviewed by “Fencesitter” and “Worried” mothers. Based on their differential feedback, separate brochures for each of these groups were subsequently developed so that the information presented matched the beliefs and concerns prominent among mothers in each group. Assessment of the revised, and now targeted (i.e., developed specifically for a population subgroup), versions of the brochures were significantly more acceptable to both groups of mothers than the original, generic, untargeted versions.<sup>86</sup>

*Finding an immunization champion.* Media have played a large role in enforcing and disseminating views related to vaccine hesitancy and refusal.<sup>87-93</sup> Within this context, the anti-vaccine movement has benefited from the participation of several notable celebrities that have actively propagated anti-vaccination messages. Their success can be attributed to a fundamental concept from social marketing—namely that messages are more influential and acceptable when the “messenger” is perceived as likeable, trustworthy and working toward the same goal as the intended audience for the message.<sup>94</sup> Indeed, in a 2009 national study of parents, 24% indicated they trusted celebrities “some” and 2% “a lot” for providing vaccine safety information.<sup>95</sup> Unfortunately, the pro-vaccination movement has not received endorsements by similarly influential celebrities, which could do much to bolster the public’s views about the necessity and safety of childhood vaccines by reiterating social norms that are more accepting of vaccination.

*Vaccine developments.* Additional strategies to minimize vaccine hesitancy could target vaccine development and administration. For example, finding ways to further combine vaccine

antigens into a single vaccine dose could allay VHP's fears about "too many shots overwhelming the immune system." Implementing evidence-based pain control techniques could minimize VHP's reluctance for vaccination because of the pain associated with vaccines. For certain vaccines, possible changes to the vaccine administration route and schedule may further address VHPs concerns. For example, the development of intranasal or oral vaccines may further minimize concerns about pain and injection-site side effects. In addition, studies are underway currently examining the efficacy of 2 doses of HPV vaccine instead of 3,<sup>96-98</sup> and some clinicians are interested in the possibility of giving HPV vaccines earlier in childhood as a way to minimize its association with sexual activity. As additional vaccines are added to the recommended schedule in the future, it may become increasingly important to consider how to leverage factors such as these to address the concerns of VHPs.

## Conclusion

Parental hesitancy for recommended childhood vaccines is a growing public health concern influenced by factors at the personal, vaccine and environmental levels. While some strategies to mitigate the trend of increased vaccine hesitancy have been identified and are already in place, additional interventions are needed - particularly to combat the growing trend of negative public and parental attitudes and unjustified fears about vaccines. Promising approaches include developing information technology to provide tailored immunization education materials that match each person's unique needs, finding immunization champions that can resonate with parents on a personal level, and leveraging characteristics of the vaccine or the vaccination schedule to minimize the concerns of vaccine hesitant parents.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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# **EXHIBIT 272**



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## “Everybody just wants to do what’s best for their child”: Understanding how pro-vaccine parents can support a culture of vaccine hesitancy

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### Abstract

**Background**—Although a large majority of parents vaccinate their children, vaccine hesitancy has become more widespread. It is not well understood how this culture of vaccine hesitancy has emerged and how it influences parents’ decisions about vaccine schedules.

**Objective**—We sought to examine how attitudes and beliefs of parents who self-report as pro-vaccine are developed and contribute to immunization decisions, including delaying or spacing vaccines.

**Methods**—Open-ended, in-depth interviews (N=23) were conducted with upper-middle class parents with young children living in Philadelphia. Interview data were coded and key themes identified related to vaccine decision-making.

**Results**—Parents who sought out vaccine information were often overwhelmed by the quantity and ambiguity when interpreting that information, and, consequently, had to rely on their own instinct or judgment to make vaccine decisions. In particular, while parents in this sample did not refuse vaccines, and described themselves as pro-vaccine, they did frequently delay or space vaccines. This experience also generated sympathy for and tolerance of vaccine hesitancy in other parents. Parents also perceived minimal severe consequences for deviating from the recommended immunization schedule.

**Conclusion**—These findings suggest that the rise in and persistence of vaccine hesitancy and refusal are, in part, influenced by the conflicts in the information parents gather, making it difficult to interpret. Considerable deviations from the recommended vaccination schedule may manifest even within a pro-vaccine population due to this perceived ambiguity of available information and resulting tolerance for vaccine hesitancy.

### Keywords

vaccine hesitancy; vaccination; parents; immunization schedule

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Conflicts of interest: None

## INTRODUCTION

The 2014–2015 measles outbreak, in which 129 people from 7 states in the US were reported to have measles linked to Disneyland in California, has highlighted the resurgence of vaccine-preventable childhood diseases previously all but eliminated in the US by the implementation of the routine child immunization schedule (1,2). While nationally the coverage of measles vaccination is high (3), the resurgence of measles, with 668 cases in 2014 and 178 in 2015 as of June, points to the risk of social or spatial clusters of undervaccinated children (1,4,5). It also sheds light on rising parental vaccine hesitancy and refusal in the United States, as evidenced by increasing exemptions from mandated immunizations for school-entry and parental requests for alternative childhood immunization schedules (6–10).

Parental vaccine decision-making has been studied extensively to understand vaccine hesitancy and alternative vaccination schedules (8,11–17). Nationally, coverage for most childhood vaccines is high, indicating that most parents choose to vaccinate children (3). However, more and more concerns are being raised about the safety of the immunization schedule given controversies about the connection between vaccines and autism, the ingredients in vaccines, and the number of injections given to children (11). A 2010 survey given to a random sample of households found that while the majority of parents intended to vaccinate their children, most of them also had questions or concerns about vaccines (11). A 2009 study of health care providers found that 43% and 28% of physicians thought parents' level of concern about vaccines had greatly or moderately increased, respectively, compared to five years before (7). These doubts manifest themselves on a spectrum of vaccine decision-making that may then lead to deviance from the recommended Advisory Committee on Immunization Practices (ACIP) immunization schedule (12,18).

A number of studies have found that common reasons for forgoing or delaying vaccines include: concern about vaccine safety or efficacy; the necessity of vaccines; the perception that the child was too young; or the child being sick (14,16,19). Common parental concerns about vaccinations include child's pain or anxiety during immunization; short-term side effects of immunization; vaccine safety; immune system overload; and number of vaccines received (15). However, external factors also mediate vaccine concerns and behavior. Studies show that trust in the doctor is an important factor in parents' confidence and decision to vaccinate (12,20). Furthermore, immunization decisions are influenced by social norms and by the behavior and attitudes of peers (11,21,22).

The vast majority of parents continue to vaccinate their children according to the ACIP-recommended schedule, suggesting belief in the benefits of vaccination and trust in the advice from health care providers. However, vaccine hesitancy and questions about the instituted immunization schedule have become more common as parents continue to raise doubts and concerns about vaccines. In this context, the goal of the current study is to understand how parents make vaccination decisions, how their vaccine concerns translate into deviations from the ACIP schedule despite general acceptance of vaccines, and how they view others' decisions not to vaccinate. Elucidating these phenomena can help explain

the rise in and persistence of vaccine hesitancy and refusal that have contributed to events like the Disneyland measles outbreak.

## METHODS

### Participants and data collection

This qualitative study used semi-structured interviews to understand how parents make decisions about child vaccination, and the attitudes, perceptions and beliefs underlying these decisions. We used convenience sampling to recruit parents in an upper-middle class neighborhood in Philadelphia. We chose this neighborhood for three reasons: 1) the relatively high socioeconomic status meant that at least some parents would be likely to report vaccine hesitancy or refusal (16,23); 2) the neighborhood is served by a pediatrician who accommodates alternative vaccine schedule requests and with whom we had conducted clinic-based studies (24); and 3) an active neighborhood parent listserv facilitated recruitment. We did not target parents based on vaccine behavior. A total of 23 interviews were conducted by two of the authors (YB, AB) between July and September 2010, a year with a particularly large number of pertussis and mumps cases (25). 25 participants (19 mothers and 2 couples) who had at least one child aged 18 months–6 years and were living in Philadelphia were interviewed. Participants provided written consent to audio-record the interviews and provided their age, educational attainment, race-ethnicity, zip code of residence, and birth year of child(ren). Interviews lasted an average of 35 minutes. Participants were given a \$20 gift card to a local natural foods supermarket as a thank you. This study was approved by the Institutional Review Board of the University of Pennsylvania.

The goal of the interview was to elicit a narrative about parental experiences of vaccination and vaccine-related decisions. The interview guide (see Table 1) consisted of open-ended questions about their child's health and temperament; a recent health-related decision; the decision process around child vaccination, including information gathering, discussion with others, and interactions with health care providers; the actual experience of vaccination; and attitudes and perceptions about other parents' vaccine beliefs and behaviors. Interviews were audio-recorded and transcribed verbatim.

### Coding and Thematic Analysis

We used a modified Grounded Theory approach to analyze interview data (26). This approach allowed the research team to ensure saturation of new parental attitudes and beliefs as they came up during the interviews (27). After the first 10 interviews were transcribed, the research team discussed emerging content codes and drafted a preliminary coding scheme. As further interviews were completed, this codebook was expanded and refined. Codes identified major content areas of the interview transcriptions, including information about the parent and child; parental decision-making; vaccine beliefs and behaviors, etc. After 23 interviews were completed, at which point thematic saturation was reached, 3 transcripts were selected at random and independently coded by two members of the research team (YB, AB) to verify coding reliability; minor changes to the codebook resulted. The research team then coded all interview data with a final codebook using NVivo 8.0

(QSR International Pty Ltd, Victoria, Australia). The first author (EW) then developed code memos which identified key themes related to the underlying study questions. Analysis of emergent themes was discussed and validated by the research team.

## RESULTS

We interviewed 21 mothers and 2 mother-father pairs from Philadelphia, Pennsylvania for a total of 23 interviews (hereafter, we refer to all interview subjects as “parents”). Parent ages ranged from 32 to 46 with a median of 36; the sample was 69% non-Hispanic white, 22% Asian; and 9% Hispanic. All participants had some higher education, including 83% with a graduate degree and 17% with a college degree (see Table 2). All parents reported discussing vaccine decisions with a spouse or partner; the mothers expressed that they were primarily the parent who sought information about vaccines, had vaccine-related conversations with other parents and with health-care providers, and took their children to doctor’s appointments. No parents in the sample declined all vaccines; 2 (23%) declined some vaccines; 9 (39%) delayed some vaccines due extenuating circumstances at the time of a vaccine appointment (e.g., the child was sick) and 10 (44%) had deliberately spaced out some vaccines. Of the 14 participants who reported following the ACIP schedule, 4 had nevertheless delayed or spaced out vaccines.

Our thematic analysis revealed important potential mechanisms that illustrated how a climate of tolerance and accommodation for vaccine refusal can arise, even in a pro-vaccine population: First, parents contemplating vaccination felt frustrated by the overwhelming and conflicting information presented by various sources. Second, their decision process was informed by a palpable tension between a “scientific” and “non-scientific” approach to decision-making. These two factors, at play during the *formation* of vaccine intentions, led many parents to *implement* a delayed or spaced schedule despite self-identifying as pro-vaccine, and as adhering to the recommended schedule. Finally, these experiences during the formation and implementation of vaccine intentions generated sympathy and tolerance for vaccine hesitancy and refusal in other parents. We elaborate on these mechanisms below (see Table 3 for representative quotations).

### Forming Vaccine Intentions

**Responding to overwhelming and conflicting information—**When describing their decision-making process around vaccination, parents reported being very well-informed, with many conducting their own research to inform their vaccination decisions. Rather than defaulting to vaccination as recommended by their pediatrician, parents made a conscious decision to vaccinate based on the available evidence.

However, parents expressed frustration at the overwhelming quantity of information available as well as perceived conflicting information from multiple sources. This led to ambiguity and uncertainty when interpreting that information. Parents cited many information sources used during their research: the scientific literature, the CDC website, books, a vaccine class, television shows, etc. Although confident about their data gathering and synthesis skills, the diversity and discrepancy across sources made it challenging (and time-consuming) to make an unequivocal decision.

### **Tension between “science-based” and “non-science-based” decision-making**

—The “information overload” experienced by parents contributed to a tension between science-based and non-science-based judgments in parents’ description of the decision-making process. In particular, while parents knew the link between autism and vaccines had been scientifically discredited, they were still influenced by the media hype, which had generated doubts and fears in the back of their minds that were difficult to silence. Whether it was concerns about autism, thimerosal, aluminum, potential allergens, or side effects of MMR, parents felt “caught up in the insanity” (Interview 5).

A common concern that parents acknowledged was not necessarily scientific was “packing in” multiple vaccines all at once. Some associated getting vaccines with “putting...diseases into this tiny person’s body” (Interview 15). Receiving too many at once felt like “overloading” or “overwhelming” the immune system of a “little” or “tiny” baby (Interviews 1, 2, 14, 15, 22, 23). The resulting decision to stagger or space vaccines, as one interviewee noted, was not based on scientific evidence, but simply seemed like a “better idea” (Interview 21).

Another issue with incorporating science in their decision-making capacities was the uncertainty in weighing the costs and benefits of vaccines. On one hand, some parents saw these childhood infectious diseases as not severe if contracted; on the other hand, it would be “detrimental” (Interview 2) if they were to have a child who reacted severely to a vaccine, albeit this was a small chance. To one parent, it was a lose-lose situation, as she would never be able to forgive herself if her baby died of whooping cough “knowing that there’s something out there that could save them,” or if the baby developed “something preemptively that we learn later, had we never done this,” thus expressing her belief in the uncertainty of the risks of vaccines (Interview 7). In addition, another parent questioned whether it was necessary to vaccinate a young child for something he or she would be unlikely to get, like Hep B, or whether it was just “convenient to do it all in the first two or three years” (Interview 6).

### **Implementing Intentions**

**Delaying or spacing out vaccines as a response to vaccine doubts**—In the face of this overwhelming uncertainty and hesitation, three main responses emerged. About a third of the parents trusted their pediatricians entirely and followed the recommended schedule. As one parent put it, “if we were going to use this particular pediatrician, what’s the point of having a relationship with them and not taking their suggestions?” (Interview 8). Another parent admitted to being nervous about “multiple shots at once,” but trust in the pediatrician overruled any other emotions affecting the decision (Interview 1). This response was consistent with articulating a belief in evidence-based reasons underlying the vaccination schedule.

A second group of parents also self-identified early in the interview as following the recommended vaccination schedule, but later reported altering the vaccine schedule due to day-of factors, like the child being sick or not wanting the child to receive too many shots at once. These parents did not perceive these deviations from the ACIP recommendation as a



“big deal” (Interview 5, 18), and report that for the most part their health care providers had no issue with accommodating the request.

A third group of parents decided to space or delay vaccines, and requested this schedule with their pediatrician up front. Parents were aware of their self-efficacy in doing so, and in fact acknowledged requesting an alteration to the schedule in order to assert that power. As one parent noted, “I wanted to know that I had control over the vaccine schedule, not [the pediatrician] or the CDC” (Interview 2). Parents requesting an altered schedule articulated specific reasons for doing so, including: not considering Hep B a necessary vaccine for a baby; avoiding multiple vaccines at once that might cause an unlikely but potential “inflammatory brain response” (Interview 6); and giving the child time to “process” the “mercury,” “aluminum,” and “other toxins” (Interviews 7, 12). Some parents noted that the reason why so many vaccinations are packed into the beginning is that “sometimes they don’t see these babies again” (Interview 11) –a category of parents they did not see themselves fall into. Regardless of how the vaccine decision was made, parents generally felt that delaying or spacing out vaccines was not at all irresponsible and even reasonable as long as the child eventually received all vaccines.

Given these doubts, parents tended to see alternative schedules as a “down-the-middle” (Interview 7) medium between not vaccinating at all versus vaccinating strictly based on authority. Delaying or spacing vaccines was a way to either balance the overload of mixed information advocating strictly for refusal or for adherence, or to act in a space in which there was a lack of “definitive” scientific information (Interview 7).

**Sympathy and tolerance for vaccine hesitancy and refusal**—Our interview guide prompted parents to describe their views of other parents’ vaccination decisions. We observed two distinct perspectives on whether and how reluctance to vaccinate should be accommodated or tolerated. Regarding vaccine *refusal*, some parents expressed strong disapproval of others who did not vaccinate their child, primarily for the harm it could cause others due to reduced herd immunity. Other parent felt neutral about others’ choices.

Regarding vaccine *hesitancy*, however, the large majority expressed some sympathy for or acceptance of others who desired an altered schedule. Parents felt that “everyone just wants to do what’s best for their child,” (Interviews 6, 13) and that doctors should be accommodating to those who do not wish to follow the schedule. While interviewees didn’t think hesitant parents were *right*, their own experiences of seemingly ambiguous and overwhelming vaccine information made decisions not to vaccinate understandable. Interviewees were particularly sensitive to the fact that hesitant parents might have, or know someone with, a child with autism or a developmental disorder, and that this first-hand experience could influence vaccine decisions. Furthermore, most interviewees did not distinguish between a spaced or delayed schedule and the recommended schedule, arguing that the social responsibility to vaccinate was fulfilled in either case.

## DISCUSSION

Our analysis of qualitative data from interviews of parents with young children revealed that they are actively engaged in the decision-making processes around their child's health and, in this sample, strongly supported vaccination. These parents nevertheless exhibited vaccine hesitancy characterized by a conflict between "science-based" and "non-science-based" decision-making capacities, exacerbated by the uncertainty they felt when interpreting these vast, and sometimes conflicting, sources of information. This produced two phenomena: first, even strongly pro-vaccine parents often altered the recommended schedule; and second, parents sympathized with and were willing to tolerate others' decisions to pursue an alternative schedule.

As in other studies, we found that high immunization rates do not necessarily imply high confidence in vaccines (11). In our parent sample, no parents outright refused vaccines for their children except in the case of HepB. However, they expressed vaccine concerns consistent with those described in studies of vaccine-hesitant or -refusing parents, including possible adverse events and the quantity of vaccines given, both overall and at one time (11,14–16,28,29). These concerns could manifest as deviations from the recommended vaccine schedule, in part to assert control over the vaccine decision, and in part to alleviate or address lingering concerns. Deviations from the schedule could also emerge less deliberately, in response to a child illness, for example, or by a gut judgment. Still, although parents might delay vaccines, they may not identify themselves this way, for example, in a structured survey.

Our results point to the importance of the pediatric primary health care provider's response to requests for schedule deviations, particularly for in-the-moment requests. Parents in our sample confirmed findings from other studies noting the importance of trust in the pediatric provider (12,16,18). We also found that parents perceived a high degree of willingness to accommodate spaced or delayed schedules, particularly when the parent had already established vaccine acceptance. Some parents reported that pediatricians themselves had suggested delaying vaccines, for example when a child was sick, to make parents more comfortable, thus endorsing and instantiating parental concerns in an altered schedule. These important parental perceptions of their providers' response to vaccine hesitancy are consistent with provider studies, which show that while pediatricians follow the AAP schedule as the default, the majority of them are willing to spread out vaccines at least sometimes, or are comfortable with an alternative schedule if requested (7,10). This illustrates the role that individual provider attitudes and behavior may have on pursuing alternative schedules especially when trying to find a way to navigate parental hesitancy without dismissing them from the practice altogether (30–32). It may also hinge on the provider's own confidence in vaccine safety, interpretation of scientific versus non-scientific information, or flexibility towards what they view as contraindications to immunization (33,34).

The phenomena identified in our analyses help explain how a culture of vaccine hesitancy has developed and persisted over the past decade. While parents may be strongly pro-vaccine, prevalent vaccine concerns in the media and within social networks can subtly

influence the implementation of vaccine intentions leading to deviations from the ACIP-recommended schedule. We found that parents who look to the published literature to inform their decision did not perceive anything wrong about delaying vaccination, as long as they were given eventually. This perception fosters an environment of tolerance for vaccine hesitant parents, which may in turn influence parents who rely on social norms for decision-making to also delay vaccinations (35). While other studies have noted the influence of social networks on parents' vaccinations decisions (21,22,36), our results identify the important role that pro-vaccine parents can play in the creation and transmission of vaccine hesitant norms through networks.

Although the degree of the impact of vaccine delay depends on how long vaccines are spaced, a delay in one vaccine may produce a domino effect in adhering to the timing of other vaccines (37). This may in turn contribute to increased risk of disease transmission and potential for outbreaks (38,39). Furthermore, pursuing alternative schedules may make children vulnerable to acquiring vaccine-preventable diseases (40). However, more studies need to be conducted on whether this depends on the type of parent on the vaccine hesitancy spectrum, and whether the degree of this epidemiological impact is negligible for vaccines delayed by minor versus severe delays.

We note several limitations in our study. First, this was a qualitative study of a specific population of parents in Philadelphia, all of whom were potentially already interested in vaccination issues. While we don't claim that their views are representative or generalizable, the parents in the sample identified qualitative themes and proposed phenomena that may help explain how pro-vaccine parents exhibit and perpetuate vaccine hesitancy, and could highlight potential issues for future studies addressing vaccine hesitancy. In addition, we base our analyses on their perceptions and recollections of vaccine decisions and provider encounters, and were not able to verify these reports. Finally, these interview data were collected in 2010. It may be that these parents' views and attitudes may have changed with new media reports on vaccines and the various disease outbreaks since 2010, or even that a new sample of parents interviewed today would have different views. However, we felt that these experiences from several years ago were still relevant in helping to explain the evolution of cultural attitudes since Wakefield and other controversies that have generated vaccine hesitancy. To investigate how attitudes have changed given the shifting landscape of vaccines and disease outbreak, we plan a follow-up study in the same neighborhood with a new cohort of parents of young kids.

## Conclusions

Parents who are pro-vaccine nevertheless exhibit vaccine hesitancy, leading them to rely on non-science-based judgments and to delay vaccinations for their children. Parents do not perceive these schedule alterations as inconsistent with pro-vaccine stance, and are in fact quite tolerant of other parents' vaccine-hesitant beliefs and decisions. The decision-making experience in the context of overwhelming and contradictory vaccine information in the media and throughout social networks may be a mechanism that generates and perpetuates a culture of vaccine hesitancy and tolerance for altered schedules, despite high rates of immunization coverage.

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## Abbreviations

ACIP	Advisory Committee on Immunization Practices
MMR	Measles-Mumps-Rubella

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**Table 1**

Interview Guide

<b>I.</b>	<b>Introduction to the interview</b>
<b>II.</b>	<b>General parental beliefs about and approaches to child health</b>
	<ul style="list-style-type: none"> <li>Tell me a little about your child(ren).                             <ul style="list-style-type: none"> <li>○ Any main health/medical issues with your child(ren)?</li> </ul> </li> <li>Tell me a bit about the last time you made a decision about your child's health?                             <ul style="list-style-type: none"> <li>○ What was the issue?</li> <li>○ Talk though how you made the decision.</li> <li>○ How did you feel about the decision you made?</li> </ul> </li> </ul>
<b>III.</b>	<b>Parental vaccine decision making</b>
	<ul style="list-style-type: none"> <li>Free-listing: List all of the words that come to mind when you hear the word "vaccine." Please try to give one word answers.</li> <li>Among the parents you know who do vaccinate their children, what reasons do they give for vaccinating?</li> <li>Among the parents you know who do not vaccinate their children or pursue an alternative schedule, what reasons do they give for that decision?</li> <li>Did you decide to vaccinate your child or children? Tell me about it.                             <ul style="list-style-type: none"> <li>○ When did you start thinking about vaccination?</li> <li>○ What prompted you to start thinking about vaccination?</li> <li>○ What sources of information did/do you seek out? Why did you use those sources?</li> <li>○ What was important to you in making the decision?</li> <li>○ Tell me about some conversations you've had with family or friends about vaccination.</li> <li>○ How do your feelings about vaccination compare with those of your partner/spouse? How do your feelings about vaccination compare with those of your friends?</li> <li>○ What messages about vaccination did/do you hear from the media?</li> <li>○ Have you changed your mind about vaccinating since your child was born? Tell me about that.</li> <li>○ What sorts of information or experiences might make you think differently about your vaccine decisions?</li> <li>○ Is there anything else you'd like to mention?</li> </ul> </li> </ul>
<b>IV.</b>	<b>Parental choice of medical provider</b>
	<ul style="list-style-type: none"> <li>How did you end up with your current doctor or pediatrician?                             <ul style="list-style-type: none"> <li>○ Has your child ever seen a different primary care provider regularly? How did you end up switching?</li> <li>○ What was important for you in choosing a doctor?</li> <li>○ How do you feel about your child's doctor as a source of information and advice about health?</li> <li>○ How important is it to you that your doctor share your views on child health issues that are important to you?</li> <li>○ How important is it to you that your friends go to or recommend your doctor?</li> <li>○ What would you do if you had a disagreement with your doctor about an important health issue?</li> </ul> </li> </ul>
<b>V.</b>	<b>Interview wrap up</b>



**Table 2**

Parents' demographic characteristics

Age range (years)	32–46 (36 median)
<b>Race</b>	
White	69.6%
Asian	21.7%
Hispanic	8.7%
<b>Highest level of education (percent) *</b>	
Bachelor's degree	17%
Graduate degree	83%
<b>Children's age range</b>	0–10
<b>Vaccination decisions</b>	
Declined all vaccines	0.0%
Declined some vaccines	8.7%
Delayed some vaccines **	39.1%
Spaced out some vaccines **	43.5%
Reported following ACIP schedule	60.9%

\* Note: All parents interviewed had a college degree or higher

\*\* Delaying means vaccines were delayed due to “day-of,” non-deliberate factors while spacing out means vaccines were deliberately and carefully spaced out

**Table 3**

Representative Quotes

Forming Vaccine Intentions	
<i>Responding to overwhelming and conflicting information</i>	
<b>Individual research and commitment to making an “informed decision”</b>	<p>“I typically question myself: why do I think this, why do I believe this, and then find research or information about why that sort of backs up my...gives me evidence to support what I’m saying. And also sort of provides counter points of view for anything that’s opposing.” (Interview 4)</p> <p>“I did my own research: I looked at, sort of, what’s in the vaccinations they were given. I looked at the various active ingredients. I looked at, kind of, the literature, the scientific literature that’s out there that talks about various things that can go wrong.” (Interview 12)</p>
<b>Making decisions from a rational, scientific perspective</b>	<p>“It seems like all of their decisions, political decisions are based on fear and so it’s a hot topic for me...I don’t want to make a decision just because I’m afraid of what the outcome may be or... without doing proper research and making an informed decision I guess. That’s really important to me to make an informed decision instead of just an anecdotal or fear based decision.” (Interview 21)</p> <p>“I think in terms of deciding whether or not to vaccinate, it’s important to gather information, but to sort of, more important than getting the information, is to understand the source of the information and you know, it’s a medical decision. It’s not an emotional decision. So you need to make a decision that’s based in science and medical fact, not in, you know, what you’re feeling or what other people are feeling.” (Interview 5)</p>
<b>Overwhelming and conflicting information; ambiguity when interpreting information</b>	<p>“Yeah, I think people are just concerned. There’s a lot out there. There’s almost too much information... So it was hard for me to decide what I should really be doing...I just felt like I couldn’t make heads or tails of all the information I had.” (Interview 2)</p> <p>“There’s just a lot of information about there about the side effects of vaccinations and I wasn’t a crazy parent where I went and read about it all.” (Interview 9)</p> <p>“I guess until they really disprove that all and they can explain why there’s such a high rate [of autism] and what the causes are, then there will always be some kind of concern that vaccinations will be linked to autism.” (Interview 3)</p> <p>“I don’t know where to find the right answer. I feel like nobody seems to really have the answer. I don’t feel that doctors really know, because if they do, are they giving all the information? Because then why are there all these books out here that say, you know, that they do need to [re]schedule, you know, these things...or even changing some of the compounds that they use to make them. You know, I just think there’s a lot of unknowns.” (Interview 7)</p> <p>“I found myself talking about it, and thinking about it, and reading about it so much that I learned a lot about how vaccines in general get developed and how the information gets distributed and how people chose to understand, you know, what they’re hearing about it. And so, um, I mean it was interesting, like the same article that I read and five other people read could have been interpreted differently.” (Interview 5).</p> <p>“There are no easy answers at this point and there are people who put information out there, whether it be about diet or vaccines or anything else that isn’t really scientifically-based...but people are, of course, looking for answers and wanting to know what happened to their child, or why did this happen, or is there a potential answer. So I think a lot of the information is misleading, too, in that regard.” (Interview 11)</p>
<i>Tension between “science-based” and “non-science-based” decision-making</i>	
<b>Too many vaccines at once</b>	<p>“I just staggered, so at least I knew her immune system wasn’t getting pummeled all at the same time.” (Interview 2)</p> <p>“But you know, they say they have these vaccines, [which] cause serious diseases. So at this point I just decided she didn’t need them all at the same time. (Interview 2)</p> <p>“And then given that [my son] was right off the bat stuck with 1,000 needles, I also felt a little bad for him. So I thought, alright, let’s give him a little break on that one.” (Interview 11)</p> <p>“I just think that if there’s any little chance that your brain has this hyper-inflammatory response because you’ve given five or six vaccines, that maybe we can just spread them out a little bit more.” (Interview 6)</p>
<b>Cost-benefit analysis and side effects</b>	<p>“I was very unsure about most of the vaccines. But most of them I felt like, I don’t know is she going to get the whooping cough? Like how bad would it be?” (Interview 2).</p>
<b>Gut reactions and fear</b>	<p>“You’re programmed now to be scared of potential autism and all these other things that could affect your baby... You can take a little bit of information from one and a little from another, but I think that’s the lesson in parenting, is that you really just have to go with your gut and take what information you want” (Interview 7).</p> <p>“I didn’t really think him having multiple shots would really do anything bad to him. I think it was just we’re around some people who chose not to vaccinate because vaccines are going to cause problems. I think it’s just sort of in the back of your mind. What if he gets all of these shots and something bad happens? I think it was just a hesitation, sort of in the back. It never has changed my behavior in any such way.” (Interview 1)</p>
Implementing Intentions	
<i>Delaying or spacing out vaccines as a response to vaccine doubts</i>	
<b>Non-science-based decisions to delay vaccines</b>	<p>“It’s nothing scientific, I just felt like it’s a very little guy. You’re giving them, and they have to digest all of this, and especially with the MMR... They get a little bit of a fever, so I thought, alright let’s have him deal with one thing and...you know I asked them, which ones of these are tougher on the kid...so let’s do that one by itself” (Interview 11).</p> <p>“I probably would have followed an alternate schedule if it had been an option just ‘cause I think spacing them out I think, like I said before and there’s no, and this is a crazy decision I guess, there isn’t really evidence suggesting it is</p>

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	more healthy or less healthy but probably, I don't know, in my mind it seems like a better idea to space them out." (Interview 21)
<i>Sympathy and tolerance for vaccine hesitancy</i>	
<b>Perceptions of vaccine refusal</b>	<p><i>Disapproval</i>  "I think sometimes parents just need to hear it, just need to be like, 'listen...I know you're paranoid with stuff but this is what you need to be doing.'" (Interview 10)  "I wrote down 'crazy people' on my list because there's just some people who are so strongly opposed to vaccination and...I don't understand it." (Interview 1)</p> <p><i>Tolerance</i>  "You know I don't think they're crazy....I would consider it more, maybe passionate or strong willed...they're taking a stand that, in a minority against a majority. They don't make these decisions lightly" (Interview 21).  "[These are] people who look at the media and maybe don't have the methods or the means to access the real literature or the real science to kind of check themselves." (Interview 6)  "Dangers associated with vaccinating your kids are really nonexistent, but I don't blame people for thinking there's something there that isn't because there's been so much misinformation and, you know the whole campaign against the MMR vaccine associated with autism and all of that. So because, you know, in the history of vaccines, there have been isolated events where there's been something in the vaccine that has gotten some people sick. I understand as a parent that there are so many things that you have no control [over], so many bad things that can happen to your kid that you have no control over that you feel like, you know, vaccinating um, is something that you can control. But sadly some parents are making the wrong decision." (Interview 5)</p>
<b>Perceptions of vaccine hesitancy and alternative schedules</b>	<p>"If you're going to do your own vaccine schedule, which is fine, then you need to keep track of it." (Interview 2)  "I think the alternate schedule's different than not vaccinating." (Interview 6)  "I'm still kind of dwelling on what kind of people give vaccines and don't give vaccines and it's hard to stereotype or label, I think, who does and who doesn't because I think everybody has their own reasoning. And, you know, you wouldn't want to judge as to why they would or wouldn't, or label them as someone who would or wouldn't, but, I think when it comes then to affect your child...that's when it's always hairy." (Interview 7)  "But in the end, like it makes you feel better, you're still vaccinating your kid. I mean, I think it has to do with the parent, you know, at this point, whatever makes them feel better about everything." (Interview 10)  "It seems like [one of the arguments] for an alternative schedule, that I kind of do believe, is that it can't be very healthy to have a whole bunch of things going into your body at the same time, a whole bunch of diseases. I'm sure you know, it's been fine for [my son] and we followed a normal schedule but I can kind of understand that rationale. But I think it's much more risky to not do it." (Interview 21)</p>

# **EXHIBIT 273**

## How Do Physicians Immunize Their Own Children? Differences Among Pediatricians and Nonpediatricians

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**ABSTRACT.** *Context.* Immunization has an essential impact on public health worldwide. Numerous studies have shown the efficacy of different vaccines to protect individuals from various diseases. However, some parents choose not to vaccinate their children for reasons such as, among others, doubts regarding their usefulness, concerns over safety or efficacy, etc. Physicians are known to exert a direct influence on immunization rates by answering questions and clarifying misconceptions. Yet, it is unknown how they immunize their own children.

*Objective.* We sought to assess how physicians interested in vaccination issues immunized, or would immunize, their own children.

*Design, Setting, and Participants.* An 11-question, Web-based survey with a total of 102 discrete answers was sent to 2070 Swiss physicians in October 2004. All physicians were subscribers to a nonprofit, Web-based expert network (InfoVac, [www.infovac.ch](http://www.infovac.ch)) that distributes monthly newsletters and answers question within 2 days on immunization issues. The InfoVac network reaches >95% of pediatricians in Switzerland but <20% of general practitioners. All responses were anonymous, and no identifier could be used to trace the participants of the survey. Questions were divided into 2 parts: (1) physicians who were parents were asked which vaccines they

gave to their own children and at what age, and (2) all physicians were asked which vaccines they would give to their own child and at what age if they had a newborn child in 2004. Vaccines available in Switzerland at the time of the survey were offered as possible replies, and recommended vaccines were considered as those noted in the Swiss federal immunization schedule issued yearly. One question compared their immunization practice between their own children and their patients. Sociodemographics, qualifying year, membership in different professional groups, and their type of practice were also requested.

*Statistics.* Standard descriptive statistics were used for sociodemographic characteristics. Univariate statistical analyses were performed for each variable to determine its relationship to the dependent variable, being a pediatrician or nonpediatrician. Logistic-regression analysis was used to calculate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs), controlling for any statistically significant demographic variables that might function as confounders (gender, parenthood, workplace, year of diploma, and type of practice). For all statistical tests, differences were considered significant at  $P < .05$ .

*Main Outcome Measure.* We performed a comparison of past and projected immunization rates in the children of pediatricians and nonpediatricians.

*Results.* One thousand seventeen valid questionnaires were received (response rate: 49.1%; pediatricians: 53.3%). Nine hundred fifteen physicians (90%) had  $\geq 1$  child. All physicians reported immunizing children in their practice. Pediatricians were more likely to be women and to work in private practice than nonpediatricians but less likely to belong to a self-reported alternative medicine association. Among the nonpediatricians, 317 were general practitioners, 144 were internists, and 95 were other specialists. Ninety-two percent of pediatricians followed the official immunization recommendations for their own children. In contrast, after controlling for gender, workplace, type of practice, and year of diploma, nonpediatricians were more likely not to have immunized their children against measles, mumps, hepatitis B, or *Haemophilus influenzae* type b. They more frequently postponed diphtheria-tetanus-pertussis (DTP) (OR: 4.5; 95% CI: 2.0–10.19) and measles-mumps-rubella (MMR) vaccination. Although projected immunization rates were higher than effective rates, 10% of nonpediatricians would still not follow the official immunization recommendations in 2004. They would more frequently refrain from using combination vaccines and postpone DTP and MMR immunization to later in life. Several comparisons confirmed the weaker use of the more recently licensed vaccines by nonpediatricians. In addition to vaccines currently recommended in Switzerland, both groups of physicians added hepatitis A, influenza, and varicella vaccines to the vaccination

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schedule of their own children. Pediatricians were more likely to give pneumococcal (OR: 2.26; 95% CI: 1.004–4.68) and meningococcal C (OR: 2.26; 95% CI: 1.62–3.17) vaccines to their own children. In contrast, they were less likely to give tick-borne encephalitis virus vaccine (OR: 0.65; 95% CI: 0.44–0.95).

**Conclusions.** Ninety-three percent of the surveyed physicians agree with the current official vaccination recommendations and would apply them to their own children. However, the observation that 5% of nonpediatricians would not use *Haemophilus influenzae* type b vaccine if they had a child born in 2004 is unexpected and concerning. In contrast, both groups gave additional vaccines than those recommended to their own children. Among physicians in Switzerland interested in immunization, a significant proportion of nonpediatricians decline or delay the immunization of their own children with the recommended MMR- or DTP-based combination vaccines, which indicates that clarification of misconceptions such as fear of “immune overload” has not yet reached important targets among health care providers who thus are unlikely to answer parental concerns adequately. *Pediatrics* 2005;116:e623–e633. URL: [www.pediatrics.org/cgi/doi/10.1542/peds.2005-0885](http://www.pediatrics.org/cgi/doi/10.1542/peds.2005-0885); immunization, immunization schedule, health survey, children, recommendations, physician's role, Switzerland, measles-mumps-rubella vaccine, questionnaire, hepatitis B vaccine, diphtheria-tetanus-pertussis vaccine, safety, administration, vaccination, vaccines, guideline adherence, multivariate analysis.

ABBREVIATIONS. OR, odds ratio; CI, confidence interval; Hib, *Haemophilus influenzae* type b; TBE, tick-borne encephalitis virus; DTP, diphtheria-tetanus-pertussis; DTaP, diphtheria-tetanus-acellular pertussis; MMR, measles-mumps-rubella; IPV, inactivated polio virus vaccine; BCG, bacillus Calmette-Guerin.

Immunization has an essential impact on public health worldwide.<sup>1</sup> Numerous studies have shown the efficacy of different vaccines to protect children and adults from various bacterial and viral infections, and several diseases have been either eradicated or significantly reduced in many countries thanks to universal immunization.<sup>2</sup> Nevertheless, a number of individuals (including parents deciding for their children) do not take advantage of this preventive measure for different reasons such as doubts regarding their usefulness, concerns over safety or efficacy, philosophical or religious opinions, or vaccine cost.<sup>3–7</sup> It is well known that health care providers can influence the rates of immunization by answering parents' questions and addressing misconceptions.<sup>8,9</sup> It is also recognized that physicians can act as role models.<sup>10</sup> Personal experience with the disease and the vaccine can have a powerful impact on how convincing the physician seems to the parents.<sup>11,12</sup> However, even health care providers can sometimes have misleading beliefs about immunization and send an unclear message to parents.<sup>4,13</sup> This becomes a crucial issue in countries in which parental demands and concerns have increased to a level that compromises the success of immunization programs. This problem is illustrated best by the persistent insufficient vaccine coverage against measles leading to continual large outbreaks in several

Western European countries including Switzerland.<sup>14–18</sup>

Our study therefore aimed at interviewing physicians to evaluate how they have immunized, or would immunize, their own children and what kind of role models they provide to parents regarding immunization.

## DESIGN, SETTING, AND PARTICIPANTS

A Web-based questionnaire (Fig 1) was sent to 2070 Swiss physicians in October 2004. The list of participants' e-mail addresses was generated from the list of subscribers to InfoVac<sup>19</sup> ([www.infovac.ch](http://www.infovac.ch)), a nonprofit Web-based expert network that distributes monthly newsletters to physicians in Switzerland and answers physicians' questions on immunization issues within 24 to 48 hours. This newsletter reaches >95% of pediatricians in Switzerland, who are automatically registered at no cost, but only a minority (<20%) of general practitioners and interested physicians subscribe (for a yearly fee of \$20 US). All responses were anonymous, and no identifier could be used to trace the participants of the survey. Therefore, 1 e-mail reminder was sent 3 weeks later to encourage participation. The 11-question survey instrument, with a total of 102 discrete answers, was presented on 1 single screen to keep transmission time short and possible loss of information resulting from connection problems to a minimum. Questions were divided into 2 parts: in the first part, parent physicians were asked which vaccines (individual and combination vaccines) they gave to their children and at what age or which vaccines they chose not to administer; in the second part, they were asked which vaccines they would or would not give and at what age if they had a newborn child in 2004. One question compared their immunization practice between their own children and their patients (Fig 1, question 6). Vaccines available in Switzerland at the time of the survey were offered as possible replies, and recommended vaccines were considered as those noted in the in the Swiss federal immunization schedule<sup>20</sup> issued yearly. Open fields were included to allow free expression of the motivations behind the use or nonuse of each of the vaccines. Sociodemographics, qualifying year, membership in different professional groups, and type of practice were also asked for separately. All screens were designed to be easily read on a single screen, and check boxes provided answers for closed-ended questions. Text fields were available for answers to open-ended questions. All data were automatically transferred in a centralized database and did not have to be reentered. Published recommendations for designing Web-based surveys were followed.<sup>21</sup>

## MAIN OUTCOME MEASURES

Sociodemographic characteristics of the participants are described by using standard descriptive statistics (frequencies and means and SDs). Comparisons of baseline demographic and immunization measures were performed by using  $\chi^2$  tests for categorical data or Fisher's exact test where appropriate. Univariate statistical analyses were performed for each variable to determine its relationship to the dependent variable, being a pediatrician or nonpediatrician. Logistic-regression analysis was used to calculate adjusted odds ratios (ORs) and 95% confidence interval (CIs), controlling for any statistically significant demographic variables that might function as confounders (gender, parenthood, workplace, year of diploma, or type of practice).

For all statistical tests, differences were considered significant at  $P < .05$  or when the 95% CI did not include 1.0. SPSS 12.0.1 (SPSS Inc, Chicago, IL) statistical software was used for analyses.

## RESULTS

Questionnaires were sent by e-mail to 2070 Swiss physicians (including 860 pediatricians) registered with InfoVac. After a single e-mail reminder, 1017 valid questionnaires were received (response rate: 49.1%; pediatricians: 53.3%). Sixteen questionnaires were invalid and withdrawn: 1 was filled in by a nonphysician, 2 were duplicates, and 13 were empty surveys. Table 1 summarizes the participants' char-



# How do physicians immunize their own children?

1. Do you have children ?

- No ☐ Please go directly to question 7!
- Yes
  - < 5 years old ☐
  - 5-15 years old ☐ (several answers possible)
  - > 15 years old ☐

2. Which vaccine(s) would you give to your **own** children? (several answers possible)

- B.C.G. ☐
- Diphtheria ☐
- Tetanos ☐
- Pertussis ☐
- Polio ☐
- Hib ☐
- Measles ☐
- Rubella ☐
- Mumps ☐
- Hepatitis B ☐
- Hepatitis A ☐
- Pneumococcal ☐
- Meningococcal C ☐
- Varicella ☐
- Tick-born encephalitis ☐
- Flu ☐
- Other vaccine(s)
  1. ....
  2. ....

3. Are there 2004 recommended vaccines that you **didn't want** give to your **own** children ? (several answers possible)

- I gave all vaccines that were available at that time ☐
- I didn't give any recommended vaccines ☐
- I didn't give tetanos ☐ because: .....
- I didn't give diphtheria ☐ because: .....
- I didn't give pertussis ☐ because: .....
- I didn't give combined DTP/DTaP ☐ because: .....
- I didn't give Hib ☐ because: .....
- I didn't give polio ☐ because: .....
- I didn't give measles ☐ because: .....
- I didn't give rubella ☐ because: .....
- I didn't give mumps ☐ because: .....
- I didn't give MMR ☐ because: .....
- I didn't give hepatitis B ☐ because: .....

4. Did you decide to postpone the first dose of **DTP/DTaP** of **your own** children? (several answers possible if different for each child)

- no, immunization between approximately 2 and 6 months ☐
- yes, immunization between approximately 6 and 12 months ☐
- yes, immunization between approximately 12 and 14 months ☐
- yes, immunization > 24 months ☐
- not immunized ☐

Fig 1. InfoVac Web-based questionnaire.

acteristics. In general, the time since qualification or region of practice had no statistically significant effect on vaccine use. Nine hundred fifteen (90%) physicians had  $\geq 1$  children (24% younger than 5 years of age, 50% between 5 and 15 years, and 52% older than

15 years of age). Women were more likely to be pediatricians, and pediatricians worked more often in private practice than nonpediatricians. Pediatricians were also less likely to belong to a self-reported alternative medicine association (3.1% vs 7%;  $P =$



5. Did you decide to postpone the first dose of **measles/MMR** of **your own children**? (several answers possible if different for each child)

- no, immunization between 12 and 24 months ☐
- yes, immunization between 2 and 5 years ☐
- yes, immunization between 5 and 10 years ☐
- yes, immunization between 10 and 15 years ☐
- yes, immunization > 15 years ☐
- not immunized ☐

6. Do you think that your **own children** have been immunized **differently** then children/patients in your own practice ? (several answers possible)

- yes, my children received more vaccines ☐
- yes, my children received less vaccines ☐
- yes, my children have been immunized earlier ☐
- yes, my children have been immunized later ☐
- no, no difference ☐

7. If you were a "new parent" in 2004, **which vaccines** would you give to **your own children**? (several answers possible)

- B.C.G. ☐
- Diphtheria ☐
- Tetanos ☐
- Pertussis ☐
- Polio ☐
- Hib ☐
- Measles ☐
- Rubella ☐
- Mumps ☐
- Hepatitis B ☐
- Hepatitis A ☐
- Pneumococcal ☐
- Meningococcal C ☐
- Varicella ☐
- Tick-born encephalitis ☐
- Flu ☐
- Other vaccine(s) 1. .... 2. ....

8. If you were a "new parent" in 2004, **which combination vaccine** would you give to **your own children**? (several answers possible)

- DTaP ☐
- DTaP-IPV ☐
- DTaP-Hib ☐
- DTaP-IPV/Hib ☐
- Hexavalent ☐
- MMR ☐
- Hepatitis A/B ☐
- no combination vaccine ☐

9. If you were a "new parent" in 2004, **at what age** would you give **the first dose** of **DTaP** to **your own children** ?

- 2-4 months ☐
- 5-6 months ☐
- 7-12 months ☐
- > 12 months ☐
- > 24 months ☐
- not vaccinated ☐

Fig 1. Continued.

10. If you were a "new parent" in 2004, at what age would you give the first measles or MMR vaccine to your own children ?

- < 2 years ☐
- 2-5 years ☐
- 6-10 years ☐
- 11-15 years ☐
- > 15 years ☐
- not vaccinated ☐

11. If you were a "new parent" in 2004, are there any combination vaccines **recommended** by the Swiss vaccine schedule that you wouldn't give to your **own children** ? (several answers possible)

- I would give all recommended vaccines ☐
- I wouldn't give any recommended vaccines ☐
- no diphtheria vaccine ☐ because: .....
- no tetanus vaccine ☐ because: .....
- no pertussis vaccine ☐ because: .....
- no DTPa vaccine ☐ because: .....
- no polio vaccine ☐ because: .....
- no Hib vaccine ☐ because: .....
- no DTPa-IPV/Hib vaccine ☐ because: .....
- no hexavalent vaccine ☐ because: .....
- no measles vaccine ☐ because: .....
- no rubella vaccine ☐ because: .....
- no mumps vaccine ☐ because: .....
- no MMR vaccine ☐ because: .....
- no hepatitis B vaccine ☐ because: .....

To help us identify some factors that might influence the way physicians immunize their own children, please answer to the following questions :

You are : (several answers possible)

- a man ☐
- a woman ☐
- a pediatrician ☐
- a general practitioner ☐
- an internist ☐
- another specialist ☐

You finished your medical school :

- $\geq$  2000 ☐
- between 1990-1999 ☐
- between 1980-1989 ☐
- between 1970-1979 ☐
- between 1960-1969 ☐
- < 1960 ☐

You live in \_\_\_\_\_

(list of cantons)

You work in \_\_\_\_\_

(list of cantons)

You work : (several answers possible)

- in private practice ☐
- at a hospital ☐
- in public administration ☐
- in school medicine ☐
- in the pharmaceutical industry ☐
- other professional area : .....

Fig 1. Continued.

- SSI/SGP (Pediatric) ☐
- Forum für Praxispädiatrie (Pediatric) ☐
- SSMG/SGAM (general medicine) ☐
- CMPR/KHM (primary care medicine) ☐
- SSMI/SGIM (internal medicine) ☐
- SSI/SGInf (infectiology) ☐
- Alternative medicine association ☐

Where do you find information concerning immunization in your daily practice  
(1 to 5, 1 being the most useful) :

- documents of the Swiss Federal Office of Public Health ☐
  - documents of Forum für Praxispädiatrie ☐
  - documents prepared by the pharmaceutical industry ☐
  - documents distributed by Infovac ☐
  - other documents ☐
- (such as : .....)

We thank you for your participation and look forward to sharing the results with you.

Your InfoVac experts

Fig 1. Continued.

.027; OR: 0.473; 95% CI: 0.24–0.92). Nonpediatricians were more likely to have graduated a longer time ago, to have children, and to be from the German-speaking part of Switzerland. Among the nonpediatricians, there were 317 general practitioners, 144 internists, and 95 other specialists. All physicians reported immunizing children in their practice.

Overall, immunization rates reported by physicians for their own children were very high. This was true for all vaccines but was especially striking in

immunization rates for measles (95.7%), rubella (95.1%), and mumps (93.8%). When asking pediatrician parents ( $n = 392$ ) which individual recommended vaccines they gave to their own children (Table 2), they were more likely to have given *Haemophilus influenzae* type b (Hib) (OR: 1.5; 95% CI: 1.001–2.14), measles (OR: 3.1; 95% CI: 1.3–7.2), mumps (OR: 1.97; 95% CI: 1.05–3.7), and hepatitis B (OR: 1.48; 95% CI: 1.07–2.05) vaccines than nonpediatrician physician parents ( $n = 523$ ). They were also

TABLE 1. Characteristics of Participating Physicians ( $n = 1017$ )

Characteristic	Pediatricians ( $n = 458$ ), %	Nonpediatricians ( $n = 559$ ), %	Statistics		
			$\chi^2$	$df$	$P$
Gender					
Female	42.6	26.1	27.43	1	<.001
Have children	85.6	93.6	17.72	1	<.001
<5 y old	22.7	21.1	NS		
5–15 y old	42.4	46.3	NS		
>15 y old	41.7	50.8	8.38	1	.004
Type of activity*					
Private practice	56	48.9	37.85	5	<.001
Hospital	19.7	11.4			
Administration	1.1	3.6			
School health service	21.9	31			
Industry	0.7	2.5			
Other	0.7	2.5			
Year of medical diploma†					
>2000	1.4	0.3	29.59	5	<.001
1990–1999	13.2	12.1			
1980–1989	14.4	22.6			
1970–1979	12.5	17.3			
1960–1969	3.6	2.2			
<1960	0.4	0.2			
Region of practice‡					
French-speaking part	34.6	28	9.30	2	.01
German-speaking part	59.1	68.1			
Italian-speaking part	6.3	3.9			

NS indicates not significant.

\* Thirteen were not available.

† Seven were not available.

‡ Thirty-three were not available.

more likely to have given all recommended vaccines to their own child (OR: 2.19; 95% CI: 1.368–3.5). The comparatively lower use of Hib vaccine essentially reflected its more recent availability, because it was given to 97.3% of children <5 years old. Similarly, hepatitis B is currently recommended at 11 to 15 years of age in Switzerland, which is reflected in a significantly higher (84.8%) vaccine use by physician parents of children >15 years old.

In addition to the vaccines currently recommended in Switzerland, both groups of physicians frequently added hepatitis A, influenza, and varicella vaccines to the vaccination schedule of their own children (Table 2). Pediatrician parents were more likely to have given pneumococcal (OR: 2.17; 95% CI: 1.004–4.68) and meningococcal C (OR: 2.26; 95% CI: 1.62–3.17) vaccines to their own children. In contrast, they were less likely to have given tick-borne encephalitis virus (TBE) vaccine than nonpediatrician parents (OR: 0.65; 95% CI: 0.44–0.95).

When asked about timing of immunization, nonpediatrician parents were 4.5 times more likely to not

have administered the first dose of diphtheria-tetanus-pertussis (DTP) or diphtheria-tetanus-cellular pertussis (DTaP) combination vaccine at the recommended age of 2 to 6 months (OR: 4.5; 95% CI: 2.0–10.19). In fact, they were more likely to have given the first dose of this vaccine between 6 and 12 months of age. This remained true when looking only at parents of children younger than 5 years of age (OR: 13.27; 95% CI: 1.59–110.8). More pediatrician parents gave the measles-mumps-rubella (MMR) vaccine at the recommended schedule than nonpediatrician parents (OR: 2.78; 95% CI: 1.64–4.69). A statistically significant number of nonpediatricians (4.8%) didn't give the MMR vaccine at all to their own children. In general, pediatricians were more likely to immunize their own children than their patients (OR: 1.55; 95% CI: 1.11–2.15) and tended to immunize at an earlier age compared with nonpediatrician parents ( $P = .051$ ; OR: 2.766; 95% CI: 0.994–7.697), whereas nonpediatrician parents were more likely to give exactly the same vaccines and in

**TABLE 2.** Own Children's Vaccination in Pediatricians Versus Nonpediatricians, Controlling for Demographics ( $n = 915$ )

	Pediatricians ( $n = 392$ ), %	Nonpediatricians ( $n = 523$ ), %	$P$	Adjusted OR*	95% CI
Individual vaccines					
Recommended vaccines in Switzerland					
Diphtheria	100	99.4	NS		
Tetanus	100	99.6	NS		
Pertussis	98.7	96.9	NS		
Polio	99.2	99.4	NS		
Hib	71.4	68.8	.05	1.46	1.001–2.14
Measles	97.4	94.5	.009	3.09	1.33–7.17
Mumps	95.2	92.7	.035	1.97	1.05–3.69
Rubella	95.7	94.6	NS		
Hepatitis B	68.1	64.6	.019	1.48	1.07–2.05
Additional vaccines					
Hepatitis A	48.5	46.5	NS		
Meningococcus C	31.9	18.4	<.001	2.26	1.62–3.17
TBE	14.8	24.5	.025	0.65	0.44–0.95
Influenza	12.8	14.3	NS		
Pneumococcus	5.1	2.9	.049	2.17	1.004–4.68
Varicella	3.1	3.6	NS		
Combination vaccines					
DTP between 2 and 6 mo†	97.4	91.4	<.001	4.51	2.0–10.19
DTP between 6 and 12 mo†	1.5	4.8	.022	0.31	0.11–0.84
MMR between 12 and 24 mo†	93.6	85.7	<.001	2.77	1.64–4.69
MMR not given	0.8	4.8	.002	0.14	0.04–0.51
In general					
All recommended vaccines	91.6	85.1	.001	2.19	1.37–3.49
More vaccines than recommended	28.8	21	.009	1.55	1.11–2.15
Earlier vaccination than recommended	3.1	1.3	.051‡	2.77	0.99–7.69
No difference in timing of vaccination	65.8	72.1	.041	0.73	0.53–0.99

NS indicates not significant

\* Controlling for gender, workplace, year of diploma, and type of practice.

† First dose.

‡ Not statistically significant.



the same time frame to their own children as to their patients.

When asked which recommended vaccines they would give if they had a young child in 2004, 93.2% of the physicians agreed that they would follow the current Swiss vaccination recommendations (Table 3). Projected immunization rates were generally higher than effective rates (Table 2). This was especially noticeable in vaccines against Hib (97.8%), hepatitis B (94.8%), measles (98.5%), rubella (97.9%), and mumps (97%). There were marked differences between pediatricians and nonpediatricians: pediatricians were more likely to give Hib and hepatitis B vaccines than nonpediatricians (OR: 3.78 and 1.92, respectively, after controlling for demographics). More than 94% of all respondents agreed with using combination vaccines such as DTaP-inactivated polio vaccine (IPV)-Hib and MMR, for their child in 2004. Pediatricians were more likely to give pentavalent (DTaP-IPV-Hib), hexavalent (DTaP-IPV-Hib-Hepatitis B), and MMR combination vaccines than nonpediatricians (OR: 3.86, 1.96, and 2.81, respectively). They would also give the first doses of DTaP and MMR vaccines at a younger age ( $P = .001$  and  $P < .001$ , respectively) than nonpediatricians. Although 93.2% of all physicians agreed with following the recommendations for vaccinating their own child, nonpediatricians were twice as likely as pediatricians to deviate, for their own child, from the recommended schedule (OR: 2.02; 95% CI: 1.16–3.53). Ad-

ditional vaccines were also selected frequently by physicians in 2004 (Table 3). Pediatricians would be more likely to protect their children with pneumococcal and meningococcal C (OR: 3.04 and 2.16, respectively) vaccines. However, they would be less likely to give the bacillus Calmette-Guerin (BCG) and TBE vaccines than nonpediatricians (OR: 0.39 and 0.53, respectively).

## CONCLUSIONS

Little is known about the immunization practices of physicians regarding their own children.<sup>22</sup> The results of this study suggest that although 93% of the surveyed physicians agree with current official vaccination recommendations and would apply them to their own children, this opinion is not shared by a significant proportion of nonpediatricians who were twice as likely not to have followed (and, hypothetically, not to follow in 2004) the official recommendations for their own children.

DTP-polio-immunization rates were remarkably high in children of both groups of physicians. In contrast, Hib coverage was significantly lower. This reflected in part its more recent availability (1990), because 97.3% of the physicians with children <5 years old had protected their children against Hib. However, the observation that 5% of nonpediatricians would not use the Hib vaccine if they had a child born in 2004 is unexpected, given the severity of the disease, the high efficacy and safety of Hib

**TABLE 3.** Projected Vaccination of Own Children in 2004: Pediatricians Versus Nonpediatricians, Controlling for Demographics ( $n = 1017$ )

	Pediatricians ( $n = 458$ ), %	Nonpediatricians ( $n = 559$ ), %	<i>P</i>	OR	95% CI
Individual vaccines					
Recommended vaccines in Switzerland					
Diphtheria	99.6	97.7	NS		
Tetanus	99.6	98	NS		
Pertussis	99.1	96.6	NS		
Polio	98.9	97.9	NS		
Hib	98.7	95.2	.013	3.78	1.33–10.76
Measles	98.7	96.4	NS		
Mumps	96.5	95.5	NS		
Rubella	98	95.9	NS		
Hepatitis B	95.9	92.1	.040	1.92	1.03–3.59
Additional vaccines					
Hepatitis A	48	47	NS		
Meningococcus C	40.8	25.2	<.001	2.16	1.61–2.89
TBE	11.4	20.8	.001	0.52	0.36–0.78
Pneumococcus	18.3	7.2	<.001	3.04	1.93–4.79
Varicella	9.2	12.5	NS		
Influenza	8.7	10.4	NS		
BCG	3.7	5.9	.009	0.39	0.19–0.79
Combination vaccines					
DTaP-IPV-Hib	98.3	94.1	.003	3.86	1.59–9.4
Hexavalent	44.8	30.4	<.001	1.96	1.48–2.59
MMR	97.6	94.1	.014	2.81	1.24–6.41
DTP between 2 and 4 mo*	98.2	91.4	<.001	2.11	1.55–2.87
MMR before 2 y*	95.6	84.6	<.001	2.27	1.66–3.12
In general					
All 2004 recommended vaccines	94.8	90.2	.013	2.02	1.16–3.53

Gender, parenthood, workplace, year of diploma, and type of practice were controlled for. NS indicates not significant; hexavalent, DTaP-polio-Hib-hepatitis B combination vaccine.

\* First doses.

vaccines, and the availability of DTaP-IPV/Hib pentavalent combination vaccine, which prevents an additional shot. This observation is supported by the fact that only 94.1% of nonpediatricians (compared with 98.3% of pediatricians) would use a pentavalent vaccine for their own children in 2004. Reasons evoked by physicians declining the use of Hib vaccines for their own children included lack of awareness ("no invasive Hib disease seen in 25 years of private practice") but also reflected a subjective relative-risk analysis led by the desire to reduce vaccines to a minimum ("risk currently minimal in my area") (Table 4). It is fortunate that a 4-dose Hib-immunization schedule induces efficient herd immunity in Switzerland and elsewhere.<sup>23</sup>

Hepatitis B immunization was introduced into the Swiss immunization schedule in 1998 and is currently officially recommended at 11 to 15 years of age, and hepatitis B immunization containing hexavalent infant vaccines was introduced as an alternative in 2001. Only a minority (30.4%) of nonpediatricians would use such a hexavalent combination vaccine for their children in 2004. However, 94.8% of physicians would immunize their own children against hepatitis B in 2004, which is significantly higher than the median national immunization rate (52%) recorded in 2003.<sup>24</sup>

In contrast, observed and projected rates of MMR immunization by nonpediatricians are of concern. Although acceptance rates are much higher than in the general population (84%),<sup>25,26</sup> almost 5% of physicians in this survey did not use the MMR vaccine and would not give it to their own children in 2004. The main reasons evoked by this minority of physicians include the wish to avoid trivalent combined vaccines because of safety concerns, the preference for infection-driven rather than vaccine-induced immunity, and the conviction that homeopathic treatment allows a benign outcome of measles, mumps, and rubella. These are frequent beliefs in the general population and that they are supported by physicians who adhere to alternative medicine concepts is not unexpected.<sup>27,28</sup> The impact of misconceptions regarding MMR vaccines can be appreciated by the

recent autism–MMR-vaccine controversy, which led to a decrease in MMR immunization levels in the United Kingdom.<sup>18,29–31</sup> It therefore represents a significant threat to the World Health Organization's program to eliminate measles from the European region and may predict the persistent circulation of the measles virus and consecutive outbreaks.<sup>15–17,32</sup> Indeed, herd immunity is thought to succeed in the control of measles only when immunization levels are >93% to 95%.<sup>33</sup>

The belief that immunization may be initiated "too early" is also a frequent parental concern fueled by theoretical issues such as immune overload.<sup>3,34,35</sup> Again, almost 10% of nonpediatricians indicated that they would initiate DTaP immunization beyond the age of 4 to 6 months and 15% would not give the first dose of measles or MMR vaccine before 2 years of age, thus contributing to the maintenance of a reservoir of susceptible nonimmune young children.

A contrasting observation of this survey was the relatively frequent use of additional vaccines that physicians chose for their own children despite the lack of reimbursement. The use of hepatitis A vaccine was similar in both groups of parent physicians, probably reflecting similar travel attitudes. Pediatricians were much more likely to offer additional vaccines to their children than nonpediatricians. This was most marked for the pneumococcal conjugate vaccine, currently only recommended for high-risk groups in Switzerland, and the group C meningococcal conjugate vaccine, which possibly reflects the greater experience of pediatricians with serious outcomes of the diseases caused by these organisms and/or their greater access to information and training opportunities on these recently available vaccines.<sup>36–38</sup> The observation that nonpediatricians were 3 times more likely to select the BCG vaccine for a newborn child in 2004 despite its withdrawal from the Swiss routine-immunization schedule in 1987 indirectly suggests the importance of continuous education in vaccine-related issues. In contrast, immunization against TBE was selected twice as often by nonpediatricians, which might reflect the fact that immunization against TBE is recommended in

**TABLE 4.** Main Physicians' Reasons for Withholding Immunization in this Survey

Vaccine	Reasons for Withholding
Overall	"immune system not ready"; "immune overload"
Diphtheria	"not necessary, risk currently minimal in Switzerland"
Pertussis	"not useful, illness usually not severe"
	"vaccine linked with side effects"
Polio	"only useful when travelling: no travel, no vaccine"
Hib	"no invasive Hib disease seen in 25 years of private practice"
Hexavalent combination	"not clear if linked with severe side effects"
	"I am afraid of side effects"
	"no experience with it"
MMR	"vaccine more harmful than disease"
	"vaccine useless at young age: should be given later"
	"luxury vaccine: diseases mild"
	"only necessary in girls/women"
	"homeopathic treatment prevents disease"
Hepatitis B	"only to teenagers"
	"not sure the vaccine works"
	"only to 'at-risk' groups"
	"risk of side effects such as multiple sclerosis"

Switzerland for adults and children >6 years of age living in endemic areas, and around 50% of pediatric internists are more used to its administration than pediatricians.

Our results must be interpreted in the context of several methodologic limitations. The Web-based survey was pilot tested for usability but not validated for reliability or external validity. The first part of this survey might have been influenced by a recollection bias, because physicians were asked to remember which vaccines were given to their own children, sometimes several decades before. However, the second part explored how physicians, hypothetically, would immunize their children if born in 2004 (ie, at the time of the survey). Here, a response-effect bias is possible but unlikely because there are no "right" answers. Self-reported evaluations by physicians have already been used successfully in other areas.<sup>39</sup> Recruiting subscribers to InfoVac, a nonprofit Web-based expert group on immunization issues, and the 50% response rate introduces several obvious biases. Although the survey reached >95% of the pediatricians, the proportion of nonpediatricians was much more limited. It is most likely that subscribers to the InfoVac services, and among them survey participants, are more directly interested in immunization issues, such that our results cannot be generalized to all physicians. This is especially true for nonpediatricians who have to actively register with InfoVac. Thus, the differences observed between pediatricians and nonpediatricians answering this survey are of primary importance, because both groups are particularly interested in vaccination issues. The observation that significantly lower immunization rates were indicated by nonpediatrician parents is of concern: vaccine use could be even lower for nonpediatrician physicians who were not reached by this survey, increasing the difference between pediatricians and nonpediatricians even further.

In conclusion, 95% of pediatricians practicing in Switzerland immunize, or would immunize, their children according to recommended schedules and vaccines. They give at least as many vaccines to their own child as to their patients (and frequently many more), immunize as early as recommended, and also make a comprehensive use of the most recent combination vaccines. In contrast, a relatively large proportion of nonpediatricians do not follow, nor plan to follow, current immunization recommendations for their own children. Despite their scientific training and education, they express the same concerns as those that prevail in the public. Although this survey cannot establish the effectiveness of Swiss physicians as role models for immunization, it is known that convinced physicians are more apt to provide their patients with vaccines that they believe to be beneficial.<sup>40–43</sup> Thus, unless additional vaccine education and information efforts targeted toward these physicians eventually prove successful, the control of communicable diseases such as measles may prove impossible in Switzerland and other countries.

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## How Do Physicians Immunize Their Own Children? Differences Among Pediatricians and Nonpediatricians

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## **How Do Physicians Immunize Their Own Children? Differences Among Pediatricians and Nonpediatricians**

Klara M. Posfay-Barbe, Ulrich Heininger, Christoph Aebi, Daniel Desgrandchamps, Bernard Vaudaux and Claire-Anne Siegrist

*Pediatrics* 2005;116:e623

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# **EXHIBIT 274**

# Influenza vaccination among healthcare workers in Italy

## The experience of a large tertiary acute-care teaching hospital

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**Keywords:** Influenza, vaccine, immunization, healthcare workers

**Abbreviations:** HCWs, healthcare workers; US, United States of America ; CDC, Center for Disease Control and Prevention; ACIP, Advisory Committee on Immunization Practices ; HICPAC, Healthcare Infection Control Practices Advisory Committee

Influenza vaccination is a fundamental tool for the prevention of influenza in healthcare settings and its administration to healthcare workers (HCWs) is recommended in more than 40 countries including United States of America and many countries of the European Union. Despite these recommendations, the compliance of HCWs to influenza vaccination is largely inadequate in Italy. Since 2005/06 season, a comprehensive multifaceted intervention project aimed at increasing the seasonal influenza vaccination coverage rates among HCWs was performed at the IRCCS AOU San Martino IST teaching hospital in Genoa, Italy, the regional tertiary adult acute-care reference center with a 1300 bed capacity. Despite almost a decade of efforts, the vaccination coverage rates registered at our hospital steadily remain unsatisfactory and very distant by the minimum objective of 75% defined by the Italian Ministry of Health. During the last influenza season (2013/14), vaccination coverage rates by occupation type resulted 30% among physicians, 11% among nurses and 9% among other clinical personnel.

Further efforts are necessary to prevent the transmission of influenza to patient and novel strategies need to be identified and implemented in order to increase the compliance of HCWs, particularly nurses, with the seasonal influenza vaccination.

### Introduction

Seasonal influenza represents a major public health problem causing, each year, an increase in hospitalizations due to its complications and a substantial mortality.<sup>1</sup> Healthcare workers (HCWs), such as doctors, nurses and other health professionals may have substantial rates of clinical and sub-clinical influenza during influenza seasons and may transmit influenza to patients, many of whom have serious underlying conditions that increase the risk of complications.<sup>2</sup> Influenza illness in vulnerable patient populations, such as bone marrow transplant recipients or intensive care unit patients, can result in devastating consequences, with severe, prolonged, and often fatal disease.<sup>3</sup> Even among patients on general adult and pediatric wards, healthcare facility-acquired influenza can determine an increased length of hospital stay and added costs for testing and treatment.<sup>3</sup>

For these reasons, influenza vaccination is a fundamental tool for the prevention of influenza in healthcare settings and its administration to HCWs is recommended in more than 40 countries including the United States of America (US) and many countries of the European Union.

In the US, to protect health care workers and their patients, Center for Disease Control and Prevention (CDC), the Advisory Committee on Immunization Practices (ACIP), and the Healthcare Infection Control Practices Advisory Committee (HICPAC) recommend that all HCWs get vaccinated annually against influenza.<sup>4</sup>

In Italy, the Ministry of Health every year includes HCWs within the categories of subjects that should receive influenza vaccine in order to avoid work absenteeism during influenza season, the period with more healthcare demand, and to prevent the

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transmission of influenza from HCWs to patients, particularly to elderly or immunocompromised patients.<sup>5</sup>

In terms of vaccination coverage rate to reach in order to optimize the control of influenza in healthcare settings, in the US the Healthy People 2020 established a minimum objectives of 90% influenza vaccination coverage rate for HCWs by 2020;<sup>6</sup> in Italy, as well as in most European countries, the minimum objective to reach with the vaccination campaign is a 75% vaccination coverage rate among HCWs and the optimal goal to reach is a 95% coverage rate.<sup>5</sup> However, the vaccination coverage rates achieved in the US and in Europe are really divergent.

An internet panel survey conducted by CDC since 2010/11 influenza season among almost 2 thousands HCWs, estimated that 72% of HCWs received influenza vaccination for 2012/13 season and vaccination coverage rate resulted 92% among physicians and 85% among nurses. Interestingly, the vaccination coverage rates steadily increased during the three seasons of surveillance.<sup>7</sup>

In Europe, despite decades of efforts to encourage HCWs to be immunized against influenza, vaccination levels remain insufficient.<sup>8</sup> A recent survey reported official vaccination coverage rates collected in 10 European countries during three consecutive influenza seasons (from 2008/09 to 2010/11). The vaccination coverage rates ranged from 12%, registered in Norway and Wales in 2009/10, to 98% registered Romania in 2008/09. During season 2010/11 vaccination coverage was between 30% and 50% in England, Hungary, Portugal and Scotland. The remaining countries (France, Germany Norway, Slovenia, Spain, and Wales), with exception of Romania, reported vaccination coverage ranged between 14% and 28% in 2010/11.<sup>9</sup>

The very low vaccination coverage rates across Europe have also been confirmed by a population-based cross-sectional survey carried during two consecutive influenza seasons in the UK, Germany, Italy, France, Spain, Austria, Czech Republic, Finland, Ireland, Poland and Portugal. The coverage rates were generally

low and ranged from the lowest rate of 6.4% in Poland to 26.3% in Czech Republic, in 2007/08. In Italy the vaccination coverage rate was 12.2% in 2006/07 season and decreased to 10.9 in the next season, even if the difference was not statistical significant.<sup>10</sup>

Based on these results, increasing the vaccination coverage rate for influenza vaccination among HCWs represents a hard but essential challenge for all European countries including Italy.

Since 2005/06 season, a project aimed at increasing their vaccination coverage rates against influenza among healthcare personnel was performed at the IRCCS San Martino, IST teaching hospital in Genoa, the regional tertiary adult acute-care reference center with a 1300 bed capacity. The manuscript summarizes the main results of this project.

## Methods

A comprehensive, multifaceted intervention project based on education, promotion, and easy access to vaccination have been implemented by the medical directorate of the hospital in cooperation with the infection control team and the Hygiene Unit.

### Education

Continuing education of HCWs on the burden of influenza among high risk patients and benefits and risks of influenza vaccination have been implemented during the nine seasons period within several course about hospital acquired infections and patient safety

### Promotion

Promotion materials including advertising posters hanged up the time clocks every year at the beginning of the vaccination campaign, direct solicitation during the routine preventive medicine visit, letters sent to all medical directors, nursing administrators and quality managers of each department, explaining how and why the vaccine is recommended, have been used during each influenza season.

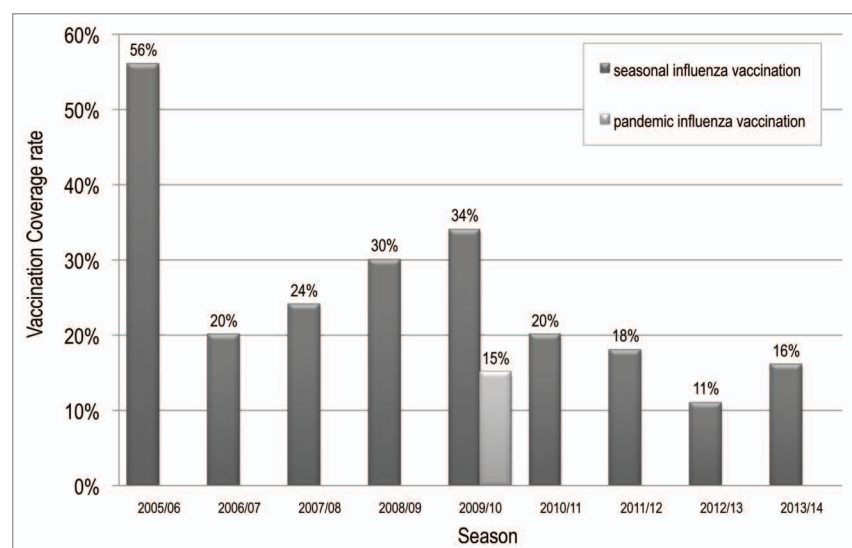
### Easy access to vaccination

The hospital has given the opportunity for health-care workers to be vaccinated at the outpatient clinics devoted to this (Hygiene Unit) as well as directly in the departments they belong to, by previous request of the necessary number of vaccine doses by fax or e-mail to the Hygiene Unit clinic.

### The pilot project in the high risk wards

Since 2013/14 influenza season a pilot project have been implemented in the high risk wards of the hospital where patients, because of their comorbidity conditions have more risk of acquiring influenza and to develop its complications. In particular the wards included in the project have been the hematological and oncological wards, intensive care units, geriatric, and general medicine wards, and pneumological wards.

The main objective of this project was to improve immunization coverage for influenza



**Figure 1.** Vaccination coverage rates among healthcare workers of IRCCS AOU San Martino, IST of Genoa during 9 consecutive seasons.

in the healthcare workers of high risk wards for nosocomial transmission of influenza.

Directly in each of the wards included in the project, the medical and nursing staff of the Hygiene Unit of the hospital have performed:

- 1) Vaccination counselling to health care personnel of the ward
- 2) Active vaccination offer and administration of vaccine
- 3) Collection of informed vaccination consent or dissent

## Results

Since the beginning of the project, vaccination coverage rates steadily increased from 20% in 2006/07 to 34% in 2009/10 (Fig. 1). In the season 2009/10 when we reached the peak of 34% in seasonal influenza vaccine coverage rate, HCWs should have been vaccinated against pandemic influenza but only 15% of our staff consented to receive the monovalent vaccine. In the following three seasons, vaccination coverage rate rapidly fell to 11% in 2012/13, while during the season 2013/14, the vaccination coverage rate among health care workers increased to 16%.

The same trend was observed among all occupation types over the eight seasons (Fig. 2). During the last season, vaccination coverage rates by occupation type resulted 30% among physicians, 11% among nurses and 9% among other clinical personnel.

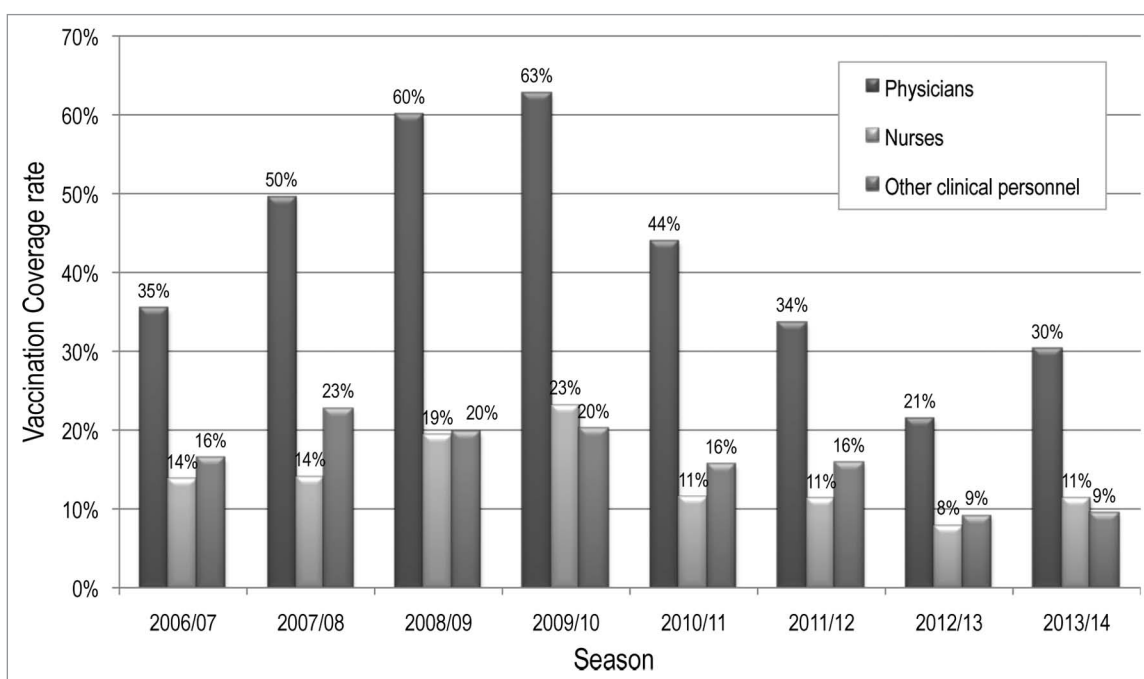
With respect to HCWs involved in the pilot project, overall 929 out of 3444 HCWs working in the hospital were included in the project and 701 (75.5%) signed the vaccination consent or dissent. The vaccination coverage rates of HCWs included and those not included in the project, overall and by occupation type, are outlined in Figure 3.

Interestingly, the difference in overall vaccination coverage rate and in the vaccination coverage rate among physicians resulted statistically significant, while no difference were registered in vaccination coverage rates among nurses and other clinical personnel.

During the project, we also observed some changes also in the setting of influenza vaccine administration. As outlined in Figure 4, since the beginning of the project, a gradual and steady growth in the number of vaccinations administered in the hospital wards has been observed with a consequent reduction of the doses administered at the Hygiene Unit outpatient clinic. During the last season, 74% of HCWs were vaccinated in the hospital wards and 26% at the Hygiene Unit outpatient clinic; however, 48.6% of HCWs that received the vaccination in the ward were included in the pilot project and were vaccinated by Hygiene Unit personnel.

## Discussion

Since 2005/06 season a comprehensive, work-site strategy that include education, promotion, and easy access to vaccination has been implemented at the IRCCS San Martino - IST teaching hospital in Genoa in order to increase seasonal influenza vaccination coverage rate among HCWs. Despite almost a decade of efforts, the vaccination coverage rates registered at our hospital steadily remain unsatisfactory and very distant by the minimum objective of 75% defined by the Italian Ministry of Health. The mean vaccination coverage rate in the period 2006–2013 was 21.6% ranging from 11% to 34%. The highest vaccination coverage rate of 56% registered in season 2005/06, the first year of



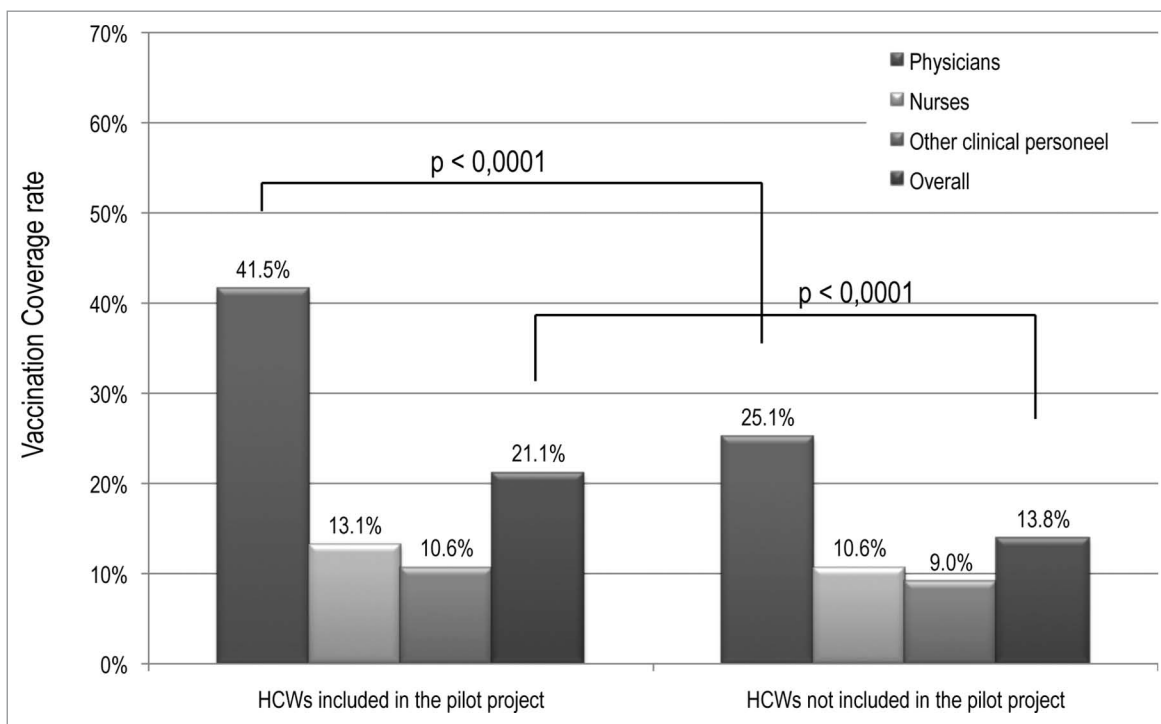
**Figure 2.** Vaccination coverage rates to occupation type among healthcare workers of IRCCS AOU San Martino, IST of Genoa during 8 consecutive seasons.



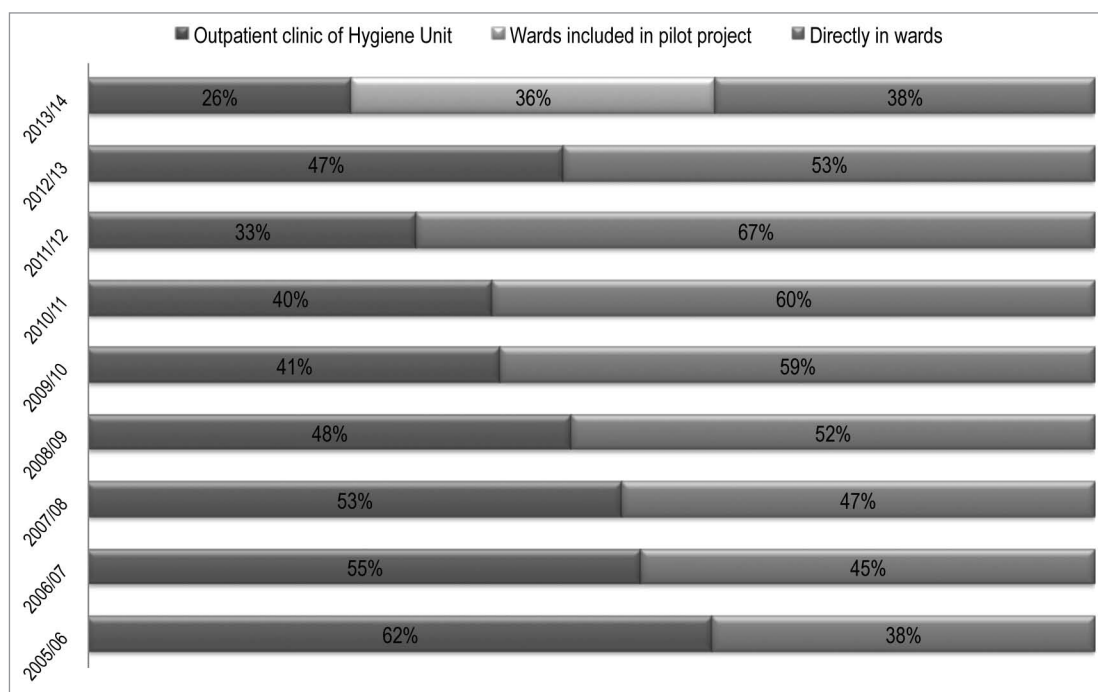
project, probably resulted by psychological conditioning related to the risk of avian influenza, whereas, during season 2012/13, when the lowest coverage rate of 11% was registered, two seasonal influenza vaccine formulations were suspended by Italian

Medicine Agency determining a shortage of influenza vaccines and raising concerns about vaccine safety.

Our data resulted in accordance with that registered in several Italian and European hospitals. During the season 2010/11, the



**Figure 3.** Vaccination coverage rates to occupation type among healthcare workers (HCWs) of IRCCS AOU San Martino, IST of Genoa included and not included in the pilot project.



**Figure 4.** Setting of influenza vaccination among healthcare workers of IRCCS AOU San Martino, IST of Genoa during 9 consecutive seasons.

mean vaccination coverage rates registered in 11 European countries was 29.8%.<sup>9</sup> In Italy, where no updated and official data are available, in the period 2006–2008 the mean vaccination coverage rate reported among HCWs was 11.5%.<sup>10</sup>

Also the decline of vaccination coverage rates observed in the post pandemic season is consistent with the results of other studies. In Germany seasonal influenza vaccine uptake in the pre-pandemic season 2008/09 was 30.5% among HCWs and decreased to 25.8% in the first post-pandemic season 2010/11.<sup>11</sup> A similar reduction was observed in France, Hungary, Portugal and Spain.<sup>9</sup>

As highlighted by other authors, the concerns about the safety, necessity and efficacy of pandemic influenza vaccination may have affected the confidence of HCWs in influenza vaccines thus contributing to decrease the seasonal vaccine uptake in the post-pandemic seasons.<sup>11,12</sup>

The results obtained during the last influenza season through vaccination counselling, active vaccination offer directly in the high risk wards and collection of vaccination dissent demonstrated a better compliance to vaccination among physicians, whereas no difference were registered among nurses and other clinical personnel. However, also the vaccination coverage rate of 41.5%, registered among physicians of high risk ward, remains suboptimal.

Overall, the results registered during the nine years project impose to identify and implement novel strategies to increase the compliance of HCWs, particularly nurses, with the seasonal influenza vaccination.

Continuing education focused on risk of influenza, benefits of vaccination and reinforcing reasons for vaccine acceptance as well as free and convenient access to vaccination over a prolonged period of time represent key component of influenza vaccination programs and should be strengthened even if their efficacy on reaching vaccination coverage rate objectives remain controversy.<sup>13,14</sup>

Visible support of institutional leadership, organization of vaccination days, gift incentives such as free food, movie tickets or health books, assignment of dedicated and specialized staff are other useful intervention components of vaccination programs.<sup>14,15</sup> Interestingly, the number of interventions included in multifaceted programs seems to be associated to the increase in vaccination uptake.<sup>14</sup>

A recent review focused on interventions to increase influenza vaccination among HCWs has pointed out that making

influenza vaccination a mandatory vaccination strategy is the most successful method for increasing vaccination uptake.<sup>14</sup> In the past few years, several healthcare facilities in the US have implemented mandatory policies achieving nearly 100% compliance.<sup>8</sup> Although mandatory policies have met considerable resistance based on the argumentation that represent a violation of fundamental individual rights, several US professional societies recommended mandatory strategy and several studies showed support for this policy among HCWs in the US.<sup>14</sup> Unlike in the US, European hospitals have been rather hesitant to implement mandatory policies.<sup>8</sup> A recent study reported the results of a multifaceted patient safety program that combined the mandatory strategy with the HCWs' right for vaccine declination. The program, which was associated with a vaccination rate of 96%, required all HCWs with direct patient contact to choose between vaccination and an "appropriate non-vaccine alternative," that is, either to wear a surgical mask or to exclude patient contact.<sup>16</sup>

## Conclusions

In our hospital, further efforts are necessary to prevent the transmission of influenza to patient. The main objective of increasing vaccination coverage rates against influenza among the healthcare personnel can be reached through well-designed long-term intervention programs that include a variety of coordinated managerial and organizational elements. In this scenario, novel strategies such as mandatory vaccination, at least in high risk wards, should be considered and debated in order to reduce the risk of nosocomial transmission of influenza in frail patients. Furthermore, a minimum vaccination coverage rate target could be included between the budget objectives of the hospital wards' clinical directors.

## Disclosure of Potential Conflicts of Interest

All authors declare that they have no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

## Acknowledgements

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# **EXHIBIT 275**

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Review

> [Infection](#). 2006 Jun;34(3):142-7. doi: 10.1007/s15010-006-5109-5.

# Influenza Vaccination of Healthcare Workers: A Literature Review of Attitudes and Beliefs

F Hofmann<sup>1</sup>, C Ferracin, G Marsh, R Dumas

Affiliations

PMID: 16804657 DOI: [10.1007/s15010-006-5109-5](https://doi.org/10.1007/s15010-006-5109-5)

## Abstract

**Background:** Influenza vaccination coverage among healthcare workers (HCW) is insufficient despite health authority recommendations in many countries. Numerous vaccination campaigns encouraging HCW to be vaccinated have met with resistance. We reviewed published influenza vaccination programs in healthcare settings to understand the reasons for their success and failure, as well as the attitudes and beliefs of HCW.

**Methods:** Relevant articles published up to June 2004 were identified in the MEDLINE/Pubmed database.

**Results:** Thirty-two studies performed between 1985 and 2002 reported vaccination rates of 2.1–82%. Vaccination campaigns including easy access to free vaccine and an educational program tended to obtain the highest uptake, particularly in the USA. Yet, even this type of campaign was not always successful. Two main barriers to satisfactory vaccine uptake were consistently reported: (1) misperception of influenza, its risks, the role of HCW in its transmission to patients, and the importance and risks of vaccination (2) lack of (or perceived lack of) conveniently available vaccine.

**Conclusion:** To overcome these barriers and increase uptake, vaccination campaigns must be carefully designed and implemented taking account of the specific needs at each healthcare institution.

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# **EXHIBIT 276**



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> [Infection](#). 2009 Jun;37(3):197-202. doi: 10.1007/s15010-008-8200-2. Epub 2008 Dec 10.

## Influenza Vaccination Compliance Among Health Care Workers in a German University Hospital

S Wicker<sup>1</sup>, H F Rabenau, H W Doerr, R Allwinn

Affiliations

PMID: 19139807 DOI: [10.1007/s15010-008-8200-2](https://doi.org/10.1007/s15010-008-8200-2)

### Abstract

**Background:** Since 1988, the Standing Committee on Vaccination (STIKO) at the Robert Koch-Institute, Berlin, has explicitly recommended that health-care workers (HCWs) should be vaccinated against seasonal influenza. However, acceptance of the influenza vaccination by medical personnel is low.

**Methods:** This study analyzes factors associated with the compliance of HCWs with the seasonal influenza vaccination on the basis of three different anonymized questionnaires during two consecutive influenza seasons: 2006/2007 and 2007/2008. The questionnaires covered details of demographics, frequency of previous vaccinations, reasons for accepting or declining the vaccination, and the HCW's knowledge of the influenza vaccine and influenza itself.

**Results:** Our study showed that physicians were significantly more likely to have been vaccinated than nurses (38.8% vs 17.4%;  $p < 0.0001$ ). The main reasons for noncompliance included: supposition of a low risk of infection, fear of side effects, the belief that the influenza vaccine might trigger the influenza virus infection, and scepticism about the effectiveness of the influenza vaccination.

**Conclusion:** Our findings confirm the importance of a comprehensive approach to the vaccination, ensuring that HCWs are correctly informed about the vaccine and that it is convenient to receive it.

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# **EXHIBIT 277**



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## Vaccine

Volume 23, Issue 24, 2 May 2005, Pages 3103-3107

# Negative attitude of highly educated parents and health care workers towards future vaccinations in the Dutch childhood vaccination program

E. Hak <sup>a</sup>  , Y. Schönbeck <sup>a</sup>, H. De Melker <sup>b</sup>, G.A. Van Essen <sup>a</sup>, E.A.M. Sanders <sup>c</sup>**Show more** <https://doi.org/10.1016/j.vaccine.2005.01.074>[Get rights and content](#)

## Abstract

### Background:

It is unknown whether further expansion of the Dutch childhood vaccination program with other vaccines will be accepted and whom should be targeted in educational strategies.

### Aim:

To determine attitudes of parents towards possible future vaccinations for their children and the behavioural determinants associated with a negative attitude.

### Design:

Questionnaire study.

## Methods:

Parents of children aged between 3 months and 5 years of day-care centres were asked to fill out a questionnaire. Determinants of a negative attitude to comply with possible future vaccinations against example diseases such as pneumonia or influenza, hepatitis B, TBC, smallpox and SARS were assessed using polytomous logistic regression analysis.

## Results:

Of the 283 respondents, 123 (43%) reported a positive attitude towards all vaccinations, 129 (46%) reported to have a positive attitude to have their child vaccinated against some diseases and 31 (11%) had no intention to comply with any new vaccination. Determinants of a fully negative attitude were a high education of the parent (odds ratio [OR] 3.3, 95% confidence interval [95% CI]: 1.3–8.6), being a health care worker (OR 4.2, 95% CI: 1.4–12.6), absence of religion (OR 2.6, 95% CI: 1.0–6.7), perception of vaccine ineffectiveness (OR 6.9, 95% CI: 2.5–18.9) and the perception that vaccinations cause asthma or allergies (OR 82.4, 95% CI: 8.9–766.8).

## Conclusion:

Modifiable determinants for a negative attitude to comply with new vaccinations are mainly based on lack of specific knowledge. These barriers to vaccinations might be overcome by improving health education in the vaccination program, especially when targeted at educated parents and health care workers.

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## Keywords

Vaccination; Child; Health education; Prevention; Infection

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# **EXHIBIT 278**

# Effects of Maternal and Provider Characteristics on Up-to-Date Immunization Status of Children Aged 19 to 35 Months

Sam S. Kim, MA, Jemima A. Frimpong, MPH, Patrick A. Rivers, PhD, MBA, and Jennie J. Kronenfeld, PhD

Childhood immunization is a widely accepted public health strategy and an indicator of adequate health care use. Vaccinations are one of the simplest and most effective approaches to protecting the health of our children.<sup>1</sup> However, immunization levels are not as high as they should be.<sup>2</sup> *Healthy People 2010* objectives call for administration of recommended vaccines to 90% or more of children by the age of 2 years and elimination of disparities in primary health key indicators, including immunizations.<sup>3–5</sup>

Recent studies show that these goals are far from being met.<sup>6,7</sup> More than 85% of children aged 19 to 35 months have been projected to have coverage for diphtheria, tetanus, and pertussis and varicella. In addition, more than 90% have been projected to have coverage for measles, mumps, and rubella (MMR); hepatitis B; and polio and approximately 73% are projected to have coverage for the 4:3:1:3 series (4 or more doses of diphtheria and tetanus toxoids and the pertussis vaccine [DTP/DT], 3 or more doses of poliovirus vaccine, 1 or more doses of measles-containing vaccine [MCV], and 3 or more doses of *Haemophilus influenzae* type b [Hib]).<sup>8–10</sup> Although these results are promising, there are disparities in immunization rates among minority and vulnerable populations. There are also inconsistencies in administration of vaccinations during children's first 2 years of life.

Many studies have examined factors that contribute to whether or not children are up to date on recommended immunizations as well as immunization compliance rates.<sup>11–14</sup> A study conducted by the Centers for Disease Control and Prevention showed that 18% of children in the United States receive the recommended vaccinations within their first 2 years of life.<sup>3</sup> Luman et al. showed that 55% of children lacked the recommended vaccinations during the first 2 years of life and that 9% received all

**Objectives.** We examined the effects of maternal and provider characteristics on the up-to-date immunization status of children.

**Methods.** We used data from the 2003 National Immunization Survey to determine variations in children's up-to-date status in the 4:3:1:3 immunization series.

**Results.** Low maternal educational levels and low socioeconomic status were associated with high 4:3:1:3 series completion rates. Also, completion rates were high in Hispanic and non-Hispanic Black families with low income-to-poverty ratios.

**Conclusions.** We found that children of less educated mothers and children in Hispanic and non-Hispanic Black families with low income-to-poverty ratios were more likely to have completed the 4:3:1:3 series. Although the reasons for these results need further exploration in other data sets, possible factors are Hispanics' positive cultural attitudes regarding the needs and importance of young children and provision of information on immunizations to low-income minority mothers who access government-subsidized health care programs. (*Am J Public Health.* 2007;97:259–266. doi:10.2105/AJPH.2005.076661)

recommended vaccinations at the recommended ages.<sup>15</sup> Hughart et al. found a strong link between the demographic characteristics of a child's family and undervaccination.<sup>16</sup> In addition, research has shown that minority children in general, but particularly minority children who live below the poverty line, are less likely than are White children to have received the recommended vaccines by age 2 years.<sup>17</sup>

Immunization rates are also affected by race/ethnicity, age, and type of vaccine. In one study focusing on children who entered kindergarten in 1992, immunization rates were examined retrospectively from the ages of 2 to 48 months. At age 16 months, 45% of non-Hispanic White children had been vaccinated, as compared with 25% of Black children, 30% of American Indian children, 30% of White Hispanic children, and 28% of Asian/Pacific Islander children.<sup>18</sup> In 2001, the Centers for Disease Control and Prevention reported that 77% of children aged 19 to 35 months were up to date on the 4:3:1:3 series.<sup>10</sup> Williams et al. reported that substandard immunization rates were most prevalent among members of disadvantaged populations.<sup>19</sup>

Some of the factors that affect whether or not children are up to date on immunizations include economic, provider, and parental variables; availability of vaccines; and vaccination policies. In addition, children in households with 2 or more other children, children with unmarried mothers having no postsecondary education, non-Hispanic Black children, children whose families use public immunization service providers, and children in families in which more than 1 physician provides immunizations are at increased likelihood of experiencing immunization delays (i.e., delays of 30 days or more above the recommended vaccination point).<sup>20</sup> Improvements in rates of compliance with national immunization guidelines are imperative. Mell et al. showed that the rate of full compliance with recommended immunization guidelines was about 35.6%, and they showed that 29.7% of children had missed opportunities for immunizations.<sup>21</sup>

Dombkowski et al. showed that children whose parents had health insurance coverage and a primary source of medical care were more likely than children with no coverage or source of care to have been vaccinated at



appropriate ages, and these factors also led to increases in up-to-date immunization rates; however, provider characteristics did not have a major influence on up-to-date status. Health insurance coverage was associated with a 13% increase in the likelihood of age-appropriate vaccination and a 2% increase in up-to-date status for MMR.<sup>22</sup> In comparing children who had a usual source of care and received at least some of their vaccinations from that source with children who did not have a usual source of care, Santoli et al. found that the former had 1.15 times the odds of being up to date for the 4:3:1:3 series.<sup>23</sup> Moreover, several studies have examined the role of maternal characteristics in immunization rates and found associations between undervaccination and maternal factors such as marital status, race, education, poverty, and age.<sup>24–28</sup> Given these findings, it is essential that system-level factors (i.e., access to a usual source of care and health insurance) and maternal factors be integrated into programs designed to improve immunization rates.<sup>22,29</sup>

The purpose of this study was to assess the effects of maternal and provider characteristics on children's up-to-date status on age-appropriate immunization series. We also expected that unforeseen factors might have effects on up-to-date status. We hypothesized that rates of completion of the 4:3:1:3 immunization series would vary according to maternal sociodemographic characteristics and number of children aged younger than 18 years in the household and that delays in completion of age-appropriate immunizations would be associated with economic barriers as well as maternal racial/ethnic background.

## METHODS

We obtained data for the study from the 2003 version of the National Immunization Survey (NIS). The NIS, sponsored by the National Immunization Program, was a random-digit-dialing nationwide household survey focusing on vaccinations.<sup>30</sup> The target population was children who were aged 19 to 35 months and living in the United States at the time their mothers were interviewed. The children covered in the 2003 survey were born between January 2000 and July 2002.

Information derived from interviews was validated via mail surveys completed by the health care providers who administered the children's vaccinations.

NIS data are gathered from 78 Immunization Action Plan areas consisting of the 50 states, the District of Columbia, and 27 large urban areas. These data provide detailed retrospective longitudinal information on vaccination completion rates and timing as well as sociodemographic characteristics of the child, mother, and family.

The original sample included 30 930 children. Our sample was selected according to the following criteria: the child had complete provider records indicating the extent to which vaccines were administered in a timely manner ( $n=13\,013$ ); household records were available showing the child's up-to-date status on the 4:3:1:3 immunization series ( $n=21\,738$ ); and there were no missing data on maternal characteristics included in the statistical analyses. We recognized that by including the first criterion just described children in our sample would have a higher likelihood of being up to date.<sup>30</sup> The final sample included 11 860 children aged 19 to 35 months.

Federal guidelines recommend that children complete the 4:3:1:3 immunization series by age 18 months.<sup>9</sup> Because all of the children in our study sample were aged 19 to 35 months, the 4:3:1:3 immunization series should have been completed by the time our data were collected. The results of preliminary analyses indicated some inconsistencies between household and provider records of children's up-to-date status. We expected such inconsistencies as well as inaccuracy of information, because not all households reported up-to-date status using information from their written vaccination record. In all of our multivariate analyses, we accounted for these discrepancies with control for information from the vaccination record. The NIS collected information about children's providers and verified up-to-date status through reviews of immunization records received directly from providers.

We constructed event indicators from a set of provider records that included a timetable of vaccine administrations with respect to birth date. In particular, we used providers' records on the timing of the fourth DTP/DT,

third polio, third Hib, and first MCV vaccines. We classified children as being up to date (according to national guidelines) on immunizations if they had been administered all of the vaccines included in the 4:3:1:3 immunization series by age 18 months. We classified children as not being up to date if they had not been administered all of the vaccinations in the 4:3:1:3 immunization series by their 18th month. We constructed a duration variable to determine the number of months between birth and completion of the 4:3:1:3 immunization series.

Characteristics assessed as predictors of up-to-date status included mother's age and educational level, race and ethnicity of child, number of children in the family aged younger than 18 years, mother's marital status, and family income-to-poverty ratio (IPR). We used child's race/ethnicity as a proxy of mother's race/ethnicity because the NIS does not report the mother's race and ethnicity. Although the NIS collects data on other variables that can be used as a proxy of mother's race/ethnicity (e.g., language in which interview is conducted), we believe that child race/ethnicity is the best alternative, assuming that all mothers are biological mothers.

We used the IPR, which compares people's income with their poverty threshold (which was determined using family income, number of persons in the household, number of children in the household, and the 2002 US Census poverty thresholds) and is expressed as a fraction, to explore possible variations in up-to-date status according to socioeconomic status. The IPR can be used not only to categorize people as above or below the poverty line but also to measure degree of poverty. An IPR of less than 1 indicates that a family is below the poverty level; an IPR of 1 indicates that a family is at the poverty level; and an IPR of greater than 1 indicates that a family is above the poverty level. We recoded raw IPR values to construct 4 categories: less than 1, 1 to 1.99, 2 to 2.99, and 3 or more.

We calculated weighted percentages for maternal and provider variables according to children's up-to-date status. We used univariate logistic regression analyses to assess variables in terms of their significance as predictors of up-to-date status. Variables shown to be significant univariate predictors, as well as

**TABLE 1—Weighted Percentages for the Maternal and Provider Characteristics Used in the Analyses for the Full Sample, by Up-to-Date (UTD) Immunization Status: US National Immunization Survey, 2003**

	Sample	UTD Status, Weighted % (SD)		P <sup>a</sup>
		Not UTD	UTD	
Mother's age, y				.001
≤ 29	45.7 (0.8)	50.7 (1.6)	44.4 (0.9)	
≥ 30	54.3 (0.8)	49.3 (1.6)	55.6 (0.9)	
Mother's educational level				.001
Less than high school	18.1 (0.7)	19.5 (1.5)	17.7 (0.8)	
High school	29.8 (0.7)	32.7 (1.6)	29.1 (0.8)	
Some college	23.2 (0.7)	24.1 (1.4)	23.0 (0.7)	
College	28.9 (0.6)	23.7 (1.2)	30.3 (0.7)	
Child's race/ethnicity <sup>b</sup>				.001
Non-Hispanic other/multiracial	8.6 (0.4)	8.3 (0.8)	8.6 (0.5)	
Non-Hispanic Black	11.4 (0.5)	16.1 (1.4)	10.2 (0.5)	
Hispanic	23.9 (0.6)	22.7 (1.4)	24.2 (0.7)	
Non-Hispanic White	56.1 (0.7)	52.9 (1.6)	57.0 (0.8)	
No. of children aged younger than 18 years				.001
≥ 4	13.3 (0.6)	19.1 (1.4)	11.8 (0.6)	
2–3	61.2 (0.8)	61.5 (1.6)	61.1 (0.8)	
1	25.5 (0.6)	19.4 (1.3)	27.1 (0.7)	
Mother's marital status				.001
Divorced/separated/widowed/deceased	7.9 (0.4)	9.9 (1.0)	7.4 (0.5)	
Never married	18.7 (0.6)	23.9 (1.5)	17.3 (0.7)	
Married	73.4 (0.7)	66.2 (1.6)	75.3 (0.8)	
Income-to-poverty ratio				.001
< 1	25.6 (0.7)	29.4 (1.6)	24.6 (0.8)	
1–1.99	25.0 (0.7)	27.9 (1.5)	24.2 (0.8)	
2–2.99	15.5 (0.5)	16.0 (1.2)	15.4 (0.6)	
≥ 3	33.9 (0.7)	26.7 (1.4)	35.8 (0.8)	
Information reported from vaccination card				.001
No	36.6 (0.7)	43.9 (1.7)	34.7 (0.8)	
Yes	63.4 (0.7)	56.1 (1.7)	65.3 (0.8)	
Provider offers comprehensive care				.004
All providers	84.7 (0.5)	80.6 (1.4)	85.7 (0.6)	
Some but not all providers	7.5 (0.4)	9.1 (0.9)	7.1 (0.4)	
No provider/provider unknown	7.8 (0.4)	10.3 (1.1)	7.1 (0.4)	
Provider offers acute illness care				.058
All providers	74.8 (0.6)	71.7 (1.5)	75.6 (0.7)	
Some but not all providers	9.4 (0.4)	10.8 (1.0)	9.0 (0.5)	
No provider/provider unknown	15.9 (0.5)	17.5 (1.3)	15.4 (0.6)	
Provider offers follow-up visits				.038
All providers	77.1 (0.6)	73.9 (1.5)	78.0 (0.7)	
Some but not all providers	9.4 (0.4)	10.6 (1.0)	9.0 (0.5)	
No provider/provider unknown	13.5 (0.5)	15.5 (1.3)	13.0 (0.6)	
Provider offers after-hours telephone services				.003
All providers	62.7 (0.7)	58.5 (1.6)	63.9 (0.8)	
Some but not all providers	10.5 (0.5)	13.2 (1.1)	9.8 (0.5)	
No provider/provider unknown	26.8 (0.7)	28.3 (1.5)	26.4 (0.8)	

*Continued*

those of obvious theoretical importance, were included in subsequent multivariate analyses.

We used the Kaplan–Meier method to calculate weighted quartile estimates of elapsed time before completion of the 4:3:1:3 series and assessed log-rank tests for equality over strata of 2 variables of theoretical importance, race/ethnicity and number of children aged younger than 18 years in the household. Using variables we had identified as possible univariate predictors, we constructed multivariate Cox proportional hazard regression models to examine whether maternal characteristics were predictive of variations in rates of children's up-to-date status on the 4:3:1:3 series. In particular, we examined how each factor contributed to delays in completion of age-appropriate immunizations. All statistical analyses were performed with SUDAAN with adjustment for the substantial oversampling of Immunization Action Plan areas and members of certain minority groups in the NIS.<sup>31</sup>

## RESULTS

Table 1 shows sample characteristics (n = 11 860) stratified according to up-to-date status, that is, by completion (n = 9510) or noncompletion (n = 2350) of the 4:3:1:3 immunization series by the age of 18 months. Forty-six percent of children in the sample had mothers who were aged 29 years or younger. A majority of the mothers either were high-school graduates or had completed more than 12 years of education. Hispanic and non-Hispanic White children made up 23.9% and 56.1% of the sample, respectively. Most children (61.2%) were from households with 2 or 3 children aged younger than 18 years; 26% resided in households with IPRs below 1. Sixty-three percent of households used information from the vaccination record to report immunization status.

Table 1 also presents the weighted percentages for provider variables, stratified according to child's up-to-date status. Most providers offered comprehensive care (84.7%), care for acute illnesses (74.8%), follow-up visits (77.1%), and after-hours telephone services (62.7%) and participated in the Vaccines for Children program (77.4%). Only 25% of providers offered Special Supplemental Nutrition

TABLE 1—Continued

Provider offers WIC program or services				.048
All providers	25.4 (0.7)	25.2 (1.5)	25.5 (0.7)	
Some but not all providers	8.9 (0.5)	11.3 (1.1)	8.3 (0.5)	
No provider/provider unknown	65.7 (0.7)	63.6 (1.6)	66.3 (0.8)	
Provider offers other services				.038
All providers	7.8 (0.4)	9.7 (1.0)	7.3 (0.4)	
Some but not all providers	6.4 (0.4)	7.1 (0.9)	6.2 (0.4)	
No provider/provider unknown	85.8 (0.5)	83.2 (1.3)	86.5 (0.6)	
Provider reports vaccines to immunization registry				.175
All providers	33.7 (0.7)	31.4 (1.5)	34.3 (0.8)	
Some but not all providers	8.8 (0.4)	9.5 (0.9)	8.6 (0.5)	
No provider	38.4 (0.7)	37.9 (1.6)	38.5 (1.6)	
Unknown	19.2 (0.6)	21.2 (1.4)	18.6 (0.7)	
Provider participates in Vaccines for Children program				.067
All providers	77.4 (0.6)	76.0 (1.4)	77.8 (0.7)	
Some but not all providers	6.3 (0.3)	7.9 (0.9)	5.8 (0.4)	
No provider	8.3 (0.4)	7.3 (0.8)	8.5 (0.5)	
Unknown	8.0 (0.4)	8.9 (1.0)	7.8 (0.4)	
Provider facility type				.184
All public	14.3 (0.5)	14.9 (1.1)	14.2 (0.6)	
All hospital	7.8 (0.4)	7.7 (0.9)	7.9 (0.5)	
All private	61.8 (0.7)	58.7 (1.6)	62.7 (0.8)	
All military/other	1.5 (0.2)	1.2 (0.3)	1.6 (0.2)	
All WIC	0.3 (0.1)	0.3 (0.2)	0.2 (0.1)	
Mixed (1 or more of these subcategories)	9.7 (0.5)	11.3 (1.1)	9.2 (0.5)	
Unknown	4.6 (0.3)	5.9 (0.8)	4.3 (0.3)	
Unweighted sample, no. <sup>c</sup>	11 860	2 350	9 510	
Weighted sample, no.	2 968 008	619 771	2 348 237	

Note. WIC = Special Supplemental Nutrition Program for Women, Infants, and Children. National Immunization Survey data include information relating to UTD status on individual vaccinations as well as several vaccination series. Information about children's providers was collected, and UTD status was verified via reviews of immunization records received directly from providers. Provider records included accurate information on vaccine administration, and age was reported in months and days. As a result of rounding, column values may not sum to 100.

<sup>a</sup>Univariate logistic regression models were used to screen for possible predictors of UTD status. Maternal characteristics with *P* values below .05 were included in subsequent multivariate analyses.

<sup>b</sup>Used as a proxy for mother's race/ethnicity.

<sup>c</sup>Reflects number of respondents included in the analysis.

Program for Women, Infants, and Children (WIC) services or other similar services. Approximately 62% of facilities were private (61.8%); only 14.8% were public.

Weighted Kaplan–Meier survival curves were assessed for number of children aged younger than 18 years in the household and child's racial/ethnic background (data not shown). Results from log-rank tests allowed us to reject the equality assumption ( $P < .001$ ). This finding partially supported our hypothesis that up-to-date rates would vary according to child race/ethnicity and

number of children aged younger than 18 years in the household.

Figure 1 shows cumulative percentages of children completing the 4:3:1:3 immunization series according to mother's race/ethnicity and household IPR. Children with Hispanic mothers and children residing in households with IPRs below 1 were most likely to have received the required immunizations at or before 18 months from birth.

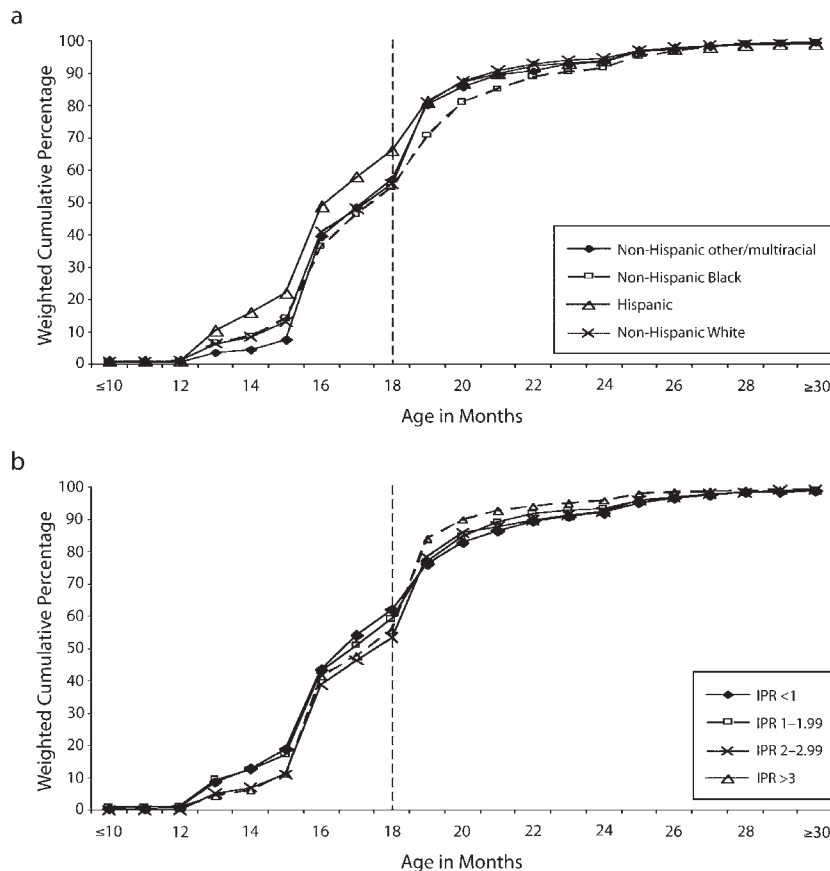
Table 2 shows hazard ratios (HRs; ratios of median survival times) and 95% confidence intervals (CIs) derived from weighted

multivariate Cox regression analyses. Longer survival times reflected delays in the timely completion of the 4:3:1:3 immunization series. Models 1 through 3 suggested that mother's age and educational level did not have any added effects on rates of 4:3:1:3 immunization series completion among Hispanics or non-Hispanic Blacks.

Model 4 showed that children of non-Hispanic Black mothers (HR=0.85; 95% CI=0.75, 0.97) were significantly less likely than children of non-Hispanic Whites to have completed the 4:3:1:3 immunization series within 18 months of their birth. Also, model 4 suggested that children of young mothers had a decreased likelihood of completing the 4:3:1:3 immunization series by this point; the completion rate was 7% lower among children of mothers aged 29 years and younger (HR=0.93; 95% CI=0.86, 0.99) than among children of mothers aged 30 years and older. Marital status and low IPR did not contribute significantly to further variability in completion rates among children of non-Hispanic Black or Hispanic mothers.

Model 6 (Table 2) shows the full model including all of the predictors assessed. Our results confirmed previous findings indicating that the presence in the household of more than 1 child aged younger than 18 years is predictive of delay in completion of the 4:3:1:3 immunization series. Completion rates in families with 4 or more children aged younger than 18 years (HR=0.68; 95% CI=0.59, 0.78) and those with 2 or 3 children (HR=0.85; 95% CI=0.79, 0.91) were 32% and 15%, respectively (the reference group in these comparisons was families with 1 child).

Lower completion rates were associated with single motherhood; the rate among children of mothers who had never been married was 14% (HR=0.86; 95% CI=0.76, 0.96), whereas the rate among children of mothers in all other marital status categories combined was 17% (HR=0.83; 95% CI=0.73, 0.96). After we controlled for other factors, completion rates were higher among children of mothers with less than 12 years of education (HR=1.16; 95% CI=1.01, 1.33) than among children of mothers with college degrees. Delays in completion were associated with IPRs above 3.



Note. Dotted line indicates 18 months from birth, the age at which the children should have completed the required immunization series.

**FIGURE 1—Weighted cumulative percentages of children up to date on the 4:3:1:3 immunization series, by race/ethnicity (a) and income-to-poverty ratio (IPR) (b): National Immunization Survey, 2003.**

In model 7 (Table 3), we tested whether or not the relationships between mother's minority status and rate of timely completion of the 4:3:1:3 immunization series varied according to differences in IPRs. We included interaction terms between mother's race/ethnicity and IPR. We found that the effects of low IPRs on timely completion were significantly different among non-Hispanic Blacks and Hispanics. In a comparison of mothers residing in households with IPRs below 1 and mothers residing in households with IPRs above 3, hazard ratios for completing the immunization series were 4% higher for those of non-Hispanic Black ethnicity (HR=1.04) and 12% higher for those of Hispanic ethnicity (HR=1.12). Relative to mothers in the reference category,

those residing in households with IPRs above 3, the hazard ratio for timely completion was 13% (HR=0.81) lower for non-Hispanic Black mothers residing in households with IPRs between 1 and 1.99.

We then assessed degrees of variation within racial/ethnic groups in rates of 4:3:1:3 immunization completion attributable to IPR. We estimated the main effects model (model 6) separately with each racial/ethnic group (data not shown). Among non-Hispanic Blacks, IPR contributed significantly to variations in completion rates. The rate of timely completion was 74% higher among non-Hispanic Blacks living in households with IPRs below 1 than among non-Hispanic Blacks living in households with IPRs above 3 (HR=1.74; 95% CI=1.17, 2.58). There were no significant

IPR-specific differences among non-Hispanic Whites or Hispanics.

## DISCUSSION

Our results suggest that the presence in a household of more than 1 child aged younger than 18 years is associated with delays in completion of recommended immunizations. We found that other predictors had varying influences on completion of the 4:3:1:3 immunization series. In particular, single motherhood significantly predicted delays in completion of appropriate immunizations. Completion rates also varied according to mothers' sociodemographic characteristics. The significant differences in immunization rates observed among non-Hispanic Blacks and Hispanics further suggest that lower rates of immunization coverage may contribute to continued health disparities in these groups.

Immunization coverage among children has increased over the years.<sup>32-34</sup> However, as indicated in this study, disparities continue in the up-to-date status of children aged 19-35 months. Other studies have shown that such disparities are increasing and thus pose a major problem in bridging the gap in immunization rates among children in different racial/ethnic groups.<sup>35,36</sup> Chu et al.<sup>35</sup> assessed immunization coverage rates among non-Hispanic White, non-Hispanic Black, Hispanic, and Asian preschool children and showed that, from 1996 to 2001, rates of inequality in coverage between non-Hispanic White and non-Hispanic Black children increased by an average of 1.1% per year, with an increase of only 0.5% per year between non-Hispanic White and Hispanic children.

If the problem of low immunization rates is to be addressed, the many factors that contribute to low rates, including missed opportunities, inadequate provider participation in WIC services, parental beliefs, and cultural factors, must be identified. In so doing, parental, provider, and system-level causes must be recognized. Once these factors have been identified, community-level intervention programs must be developed to address the role of each of these groups in existing immunization gaps as well as the role they can play in eliminating disparities.

**TABLE 2—Results of Multivariate Cox Proportional Hazard Regression Analyses (Hazard Ratios [HRs] and 95% Confidence Intervals [CIs]) Estimating Effects of Selected Characteristics on Completion of 4:3:1:3 Immunization Series: US National Immunization Survey, 2003**

	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 3, HR (95% CI)	Model 4, HR (95% CI)	Model 5, HR (95% CI)	Model 6, HR (95% CI)
Child's race/ethnicity						
Non-Hispanic other/multiracial	0.98 (0.88, 1.09)	0.98 (0.81, 1.09)	0.98 (0.88, 1.09)	0.96 (0.86, 1.07)	0.97 (0.87, 1.09)	0.97 (0.87, 1.08)
Non-Hispanic Black	0.84 (0.74, 0.95)**	0.84 (0.74, 0.96)**	0.84 (0.74, 0.96)**	0.85 (0.75, 0.97)**	0.89 (0.78, 1.02)	0.89 (0.78, 1.02)
Hispanic	1.11 (1.02, 1.21)**	1.11 (1.02, 1.22)**	1.10 (1.01, 1.21)*	1.11 (1.01, 1.22)*	1.12 (1.02, 1.23)*	1.11 (1.01, 1.22)*
Non-Hispanic White (reference)	1.00	1.00	1.00	1.00	1.00	1.00
Mother's age, y						
≤29		0.96 (0.90, 1.03)	0.97 (0.90, 1.04)	0.93 (0.86, 0.99)*	0.95 (0.88, 1.02)	0.95 (0.88, 1.03)
30 (reference)		1.00	1.00	1.00	1.00	1.00
Mother's educational level						
Less than high school			1.04 (0.91, 1.18)	1.11 (0.97, 1.25)	1.16 (1.02, 1.32)*	1.16 (1.01, 1.33)*
High school			0.86 (0.96, 1.04)	0.99 (0.91, 1.07)	1.02 (0.94, 1.11)	1.03 (0.94, 1.12)
Some college			0.99 (0.91, 1.08)	1.02 (0.94, 1.11)	1.04 (0.95, 1.13)	1.05 (0.96, 1.14)
College (reference)			1.00	1.00	1.00	1.00
No. of children aged younger than 18 years						
≥4				0.69 (0.60, 0.79)***	0.68 (0.59, 0.77)***	0.68 (0.59, 0.78)***
2–3				0.86 (0.80, 0.92)***	0.85 (0.79, 0.91)***	0.85 (0.79, 0.91)***
1 (reference)				1.00	1.00	1.00
Mother's marital status						
Divorced/separated/widowed/deceased					0.84 (0.73, 0.96)**	0.83 (0.73, 0.96)***
Never married					0.86 (0.77, 0.97)**	0.86 (0.76, 0.96)***
Married (reference)					1.00	1.00
Income-to-poverty ratio						
<1						1.01 (0.89, 1.13)
1–1.99						0.97 (0.88, 1.08)
2–2.99						0.93 (0.85, 1.02)
≥3 (reference)						1.00
Information reported from vaccination card (control variable)						
No	0.82 (0.76, 0.88)***	0.82 (0.76, 0.88)***	0.82 (0.76, 0.88)***	0.83 (0.77, 0.89)***	0.83 (0.78, 0.89)***	0.83 (0.78, 0.89)***
Yes (reference)	1.00	1.00	1.00	1.00	1.00	1.00

Note. All variables included in the multivariate models were treated as time fixed (non-time dependent). A total of 9510 children completed the vaccination series.

\* $P < .05$ ; \*\* $P < .01$ ; \*\*\* $P < .001$ .

Previous studies focusing on health care use have shown that Hispanics and members of other minority groups are less likely to use health care services than non-Hispanic Whites.<sup>37</sup> Interestingly, we found the opposite pattern among Hispanic mothers and mothers at lower educational levels. After control for mother's age, educational level, and marital status; number of children aged younger than 18 years in the household; and household IPR, the rate of 4:3:1:3

immunization completion was significantly higher among children of Hispanic mothers than among children of non-Hispanic White mothers (HR=1.11; 95% CI=1.01, 1.22). This result is noteworthy given that 72% of Hispanics in our sample lived in households with low IPRs. Interaction effects between mother's race/ethnicity and IPR further suggested that completion rates were higher in Hispanic and non-Hispanic Black families with low IPRs.

We believe that these patterns observed among Hispanic and non-Hispanic Black low-income families are probably attributable to cultural differences and government-subsidized health care programs available to such families. One important factor that we believe best explains the interactions found involves the WIC immunization requirements. Low-income minority families tend to receive WIC services more frequently than non-Hispanic White families, and they must



**TABLE 3—Full Model Including Interaction Effects Between Mother's Race/Ethnicity and Family Income-to-Poverty Ratio: US National Immunization Survey, 2003**

	Hazard Ratio (95% Confidence Interval)
Child's race/ethnicity	
Non-Hispanic other/multirace	0.98 (0.85, 1.13)
Non-Hispanic Black	0.63 (0.47, 0.84)***
Hispanic	0.97 (0.80, 1.18)
Non-Hispanic White (reference)	1.00
Income-to-poverty ratio	
< 1	0.87 (0.74, 1.01)
1–1.99	0.93 (0.83, 1.05)
2–2.99	0.92 (0.83, 1.02)
≥ 3 (reference)	1.00
Interaction effects <sup>a</sup>	
Non-Hispanic other/multiracial × IPR < 1	0.89 (0.64, 1.25)
Non-Hispanic other/multiracial × IPR 1–1.99	1.11 (0.83, 1.49)
Non-Hispanic other/multiracial × IPR 2–2.99	0.95 (0.70, 1.30)
Non-Hispanic Black × IPR < 1	1.90 (1.32, 2.74)***
Non-Hispanic Black × IPR 1–1.99	1.48 (1.01, 2.19)*
Non-Hispanic Black × IPR 2–2.99	1.20 (0.75, 1.91)
Hispanic × IPR < 1	1.33 (1.02, 1.74)*
Hispanic × IPR 1–1.99	1.13 (0.88, 1.47)
Hispanic × IPR 2–2.99	1.13 (0.84, 1.52)

Note. IPR = income-to-poverty ratio. Model 7 included all variables used in the main effects model (model 6), but parameters are not shown here. A total of 9510 children completed the vaccination series.

<sup>a</sup>Interaction terms between child's race/ethnicity and IPR.

\* $P < .05$ ; \*\*\* $P < .001$ .

comply with the program's immunization requirements. Environmental factors could have played a role as well. That is, providers in minority communities are more likely to offer WIC programs and services. The availability of clinics and community centers offering free vaccinations also could have contributed to these higher rates.

Cultural and ethnic difference in preventive health measures may further explain the higher rates of immunization coverage among Hispanics. Hispanic cultures involve strong family values, and parents tend to be more protective of their children.<sup>38</sup> Thus, the Hispanic culture's emphasis on well-being of children may amplify awareness of preventive health measures, leading to higher rates of immunization in this population.

### Limitations

In 2001, results of the NIS showed that most Hispanic parents believed immunizations should be received equally by all

children. Although percentage differences were not large, vaccination rates were highest among Hispanics; therefore, we expected that Hispanic parents would be more likely to seek adequate vaccination for their children. Although such data were not available from the NIS, it would be interesting to explore in more depth the ways in which parents make decisions about immunizations and to assess their attitudes toward health care.

Most studies that examine immunization rates are limited in that they use large volumes of cross-sectional data to measure whether up-to-date status varies in different subgroups. Our results present a more accurate description of rates of age-appropriate immunization over time. Additional studies can continue to improve our knowledge regarding disparities in immunization rates. Large national surveys, such as the one used in this study, are limited in that they do not provide detailed understandings of groups facing multiple social inequities. Our data

were also limited in that we could not examine individuals living in non-Immunization Action Plan areas, and we lacked information on Asian Americans. Future studies should address these issues.

### Conclusions

It is imperative that we focus on maternal characteristics that are barriers to immunization. It is also important that we understand, as shown by the results of this study, that less educated mothers and poor mothers from certain minority groups (in this case, Hispanic and non-Hispanic Black mothers in families with low IPRs) can be diligent in ensuring that their children received the recommended immunizations. Encouragement on the part of medical care and Medicaid providers and increased availability of such programs as Medicaid and WIC will help increase immunization rates. Providing low-income minority mothers with the necessary information about the importance of immunization can overcome lack of formal education and empower them to take advantage of the opportunities available to protect their children from preventable diseases. Interventions that target individuals and efforts to address system-level factors such as health insurance coverage and usual source of care must work in tandem if disparities in immunization are to be eliminated. ■

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### Contributors

S.S. Kim completed the analyses. J.A. Frimpong planned the study and led the writing. P.A. Rivers and J.J. Kronenfeld supervised the study and contributed to the writing of the article.

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## Human Participant Protection

No protocol approval was needed for this study.

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# **EXHIBIT 279**

For Immediate Release:  
November 18, 2013

Media Contact: Kenny Vigil  
Cell: 505-470-2290

### **Department of Health Announces Results of Vaccination Exemption Survey**

(Santa Fe) – The New Mexico Department of Health today announced results of a survey of parents who received personal religious belief vaccination exemptions on behalf of their children in 2011. This is the first survey ever conducted in New Mexico to assess parents who choose vaccination exemption, which has increased from 1,148 in 1999 to 3,372 in 2011. That's an increase of 194%.

The survey of 729 out of 2,176 eligible vaccination exemption households in New Mexico who had one or more children exempt from required school or daycare vaccination requirements in 2011 was conducted by telephone between May and July of 2013. A standardized questionnaire consisting of 60 questions was used to assess multiple domains, including the demographics of the population, knowledge, attitudes and beliefs, and parents experience with the vaccination exemption process in New Mexico.

Results indicate that parents requesting vaccination exemption in New Mexico tend to be White, non-Hispanic (74.2%), have at least a 4 year college degree (66.7%) and female (82.3%). Over half of all vaccination exemptions were in Bernalillo and Santa Fe counties (29.8% and 23.7%, respectively). The number one reason indicated for seeking a vaccination exemption was for "philosophical" or "personal belief" reasons (54.9%), which are not one of the two reasons allowed by the vaccination exemption law.

Among all respondents, 73.0% believed that many vaccine-preventable diseases can be severe. However, most believed that it is better for their child to develop immunity naturally by getting the illness rather than by getting a vaccine (59.1%) and that they could protect their child's health without vaccines (69.0%). Only 32.6% said that it is important to vaccinate their children to prevent the spread of disease in the community.

An increase in vaccination exemption is concerning because it represents a decrease in herd immunity among the population. Adequate herd immunity exists when vaccination coverage levels in a community are high enough to prevent an outbreak of a contagious, vaccine preventable disease if the disease is introduced.


All states have laws that allow for vaccine exemption, but the reasons for which exemptions are granted, and how the laws are written and interpreted, are not uniform across states. The law in New Mexico only permits vaccine exemption for medical or religious reasons.

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# **EXHIBIT 280**

# PLOS MEDICINE

## A Population-Based Evaluation of a Publicly Funded, School-Based HPV Vaccine Program in British Columbia, Canada: Parental Factors Associated with HPV Vaccine Receipt

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### Abstract

#### Background

Information on factors that influence parental decisions for actual human papillomavirus (HPV) vaccine receipt in publicly funded, school-based HPV vaccine programs for girls is limited. We report on the level of uptake of the first dose of the HPV vaccine, and determine parental factors associated with receipt of the HPV vaccine, in a publicly funded school-based HPV vaccine program in British Columbia, Canada.

#### Methods and Findings

All parents of girls enrolled in grade 6 during the academic year of September 2008–June 2009 in the province of British Columbia were eligible to participate. Eligible households identified through the provincial public health information system were randomly selected and those who consented completed a validated survey exploring factors associated with HPV vaccine uptake. Bivariate and multivariate analyses were conducted to calculate adjusted odds ratios to identify the factors that were associated with parents' decision to vaccinate their daughter(s) against HPV. 2,025 parents agreed to complete the survey, and 65.1% (95% confidence interval [CI] 63.1–67.1) of parents in the survey reported that their daughters received the first dose of the HPV vaccine. In the same school-based vaccine program, 88.4% (95% CI 87.1–89.7) consented to the hepatitis B vaccine, and 86.5% (95% CI 85.1–87.9) consented to the meningococcal C vaccine. The main reasons for having a daughter receive the HPV vaccine were the effectiveness of the vaccine (47.9%), advice from a physician (8.7%), and concerns about daughter's health (8.4%). The main reasons for not having a daughter receive the HPV vaccine were concerns about HPV vaccine safety (29.2%), preference to wait until the daughter is older (15.6%), and not enough information to make an informed decision (12.6%). In multivariate analysis, overall attitudes to vaccines, the impact of the HPV vaccine on sexual practices, and childhood vaccine history were predictive of parents having a daughter receive the HPV vaccine in a publicly funded school-based HPV vaccine program. By contrast, having a family with two parents, having three or more children, and having more education was associated with a decreased likelihood of having a daughter receive the HPV vaccine.

#### Conclusions

This study is, to our knowledge, one of the first population-based assessments of factors associated with HPV vaccine uptake in a publicly funded school-based program worldwide. Policy makers need to consider that even with the removal of financial and health care barriers, parents, who are key decision makers in the uptake of this vaccine, are still hesitant to have their daughters receive the HPV vaccine, and strategies to ensure optimal HPV vaccine uptake need to be employed.

*Please see later in the article for the Editors' Summary*

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**Competing interests:** SM is a member of the Canadian National Advisory Committee on Immunization. SD is presently a member of the British Columbia Immunization Sub-committee which advises the provincial government on practical issues related to the implementation of publicly funded immunization programs. From 2000 to 2008 SD was a member of the National Advisory Committee on Immunization for Canada. In 2008 SD attended an Advisory Board for Merck for a vaccine not yet licensed. This was not the vaccine used in the Provincial HPV vaccine program discussed in this paper. SD was paid an honorarium for my work on this advisory board.

**Abbreviations:** CI, confidence interval; HPV, human papillomavirus; iPHIS, integrated Public Health information system; TPB, Theory of Planned Behaviour

## Editors' Summary

### Background

About 10% of cancers in women occur in the cervix, the structure that connects the womb to the vagina. Every year, globally, more than a quarter of a million women die because of cervical cancer, which only occurs after the cervix has been infected with a human papillomavirus (HPV) through sexual intercourse. There are many types of HPV, a virus that infects the skin and the mucosa (the moist membranes that line various parts of the body, including the cervix). Although most people become infected with HPV at some time in their life, most never know they are infected. However, some HPV types cause harmless warts on the skin or around the genital area and several—in particular, HPV 16 and HPV 18, so-called high-risk HPVs—can cause cervical cancer. HPV infections are usually cleared by the immune system, but about 10% of women infected with a high-risk HPV develop a long-term infection that puts them at risk of developing cervical cancer.

### Why Was This Study Done?

Screening programs have greatly reduced cervical cancer deaths in developed countries in recent decades by detecting the cancer early when it can be treated; but it would be better to prevent cervical cancer ever developing. Because HPV is necessary for the development of cervical cancer, vaccination of girls against HPV infection before the onset of sexual activity might be one way to do this. Scientists recently developed a vaccine that prevents infection with HPV 16 and HPV 18 (and with two HPVs that cause genital warts) and that should, therefore, reduce the incidence of cervical cancer. Publicly funded HPV vaccination programs are now planned or underway in several countries; but before girls can receive the HPV vaccine, parental consent is usually needed, so it is important to know what influences parental decisions about HPV vaccination. In this study, the researchers undertake a telephone survey to determine the uptake of the HPV vaccine by 11-year-old girls (grade 6) in British Columbia, Canada, and to determine the parental factors associated with vaccine uptake; British Columbia started a voluntary school-based HPV vaccine program in September 2008.

### What Did the Researchers Do and Find?

In early 2009, the researchers contacted randomly selected parents of girls enrolled in grade 6 during the 2008–2009 academic year and asked them to complete a telephone survey that explored factors associated with HPV vaccine uptake. 65.1% of the 2,025 parents who completed the survey had consented to their daughter receiving the first dose of HPV vaccine. By contrast, more than 85% of the parents had consented to hepatitis B and meningitis C vaccination of their daughters. Nearly half of the parents surveyed said their main reason for consenting to HPV vaccination was the effectiveness of the vaccine. Conversely, nearly a third of the parents said concern about the vaccine's safety was their main reason for not consenting to vaccination and one in eight said they had been given insufficient information to make an informed decision. In a statistical analysis of the survey data, the researchers found that a positive parental attitude towards vaccination, a parental belief that HPV vaccination had limited impact on sexual practices, and completed childhood vaccination increased the likelihood of a daughter receiving the HPV vaccine. Having a family with two parents or three or more children and having well-educated parents decreased the likelihood of a daughter receiving the vaccine.

### What Do These Findings Mean?

These findings provide one of the first population-based assessments of the factors that affect HPV vaccine uptake in a setting where there are no financial or health care barriers to vaccination. By identifying the factors associated with parental reluctance to agree to HPV vaccination for their daughters, these findings should help public-health officials design strategies to ensure optimal HPV vaccine uptake, although further studies are needed to discover why, for example, parents with more education are less likely to agree to vaccination than parents with less education. Importantly, the findings of this study, which are likely to be generalizable to other high-income countries, indicate that there is a continued need to ensure that the public receives credible, clear information about both the benefits and long-term safety of HPV vaccination.

**Additional Information**

Please access these Web sites via the online version of this summary at <http://dx.doi.org/10.1371/journal.pmed.1000270>.

- The US National Cancer Institute provides information about [cervical cancer](#) for patients and for health professionals, including information on [HPV vaccines](#) (in English and Spanish)
- The US Centers for Disease Control and Prevention also has information about [cervical cancer](#) and about [HPV](#)
- The UK National Health Service Choices website has pages on [cervical cancer](#) and on [HPV vaccination](#)
- More information about [cervical cancer and HPV vaccination](#) is available from the Macmillan cancer charity
- [ImmunizeBC](#) provides general information about vaccination and information about [HPV vaccination](#) in British Columbia
- [MedlinePlus](#) provides links to additional resources about cervical cancer (in English and Spanish)

## Introduction

The vaccine for the human papillomavirus (HPV) is an important tool in the prevention of cervical cancer [1]–[5]. In order to maximize the benefit of the HPV vaccine for cervical cancer prevention and for programs to be cost-effective, vaccine programs should be offered to girls prior to the commencement of sexual activity [6]–[8]. Because of the age at which the HPV vaccine is given in many jurisdictions, parents will often need to provide consent. Careful reflection on parents' perspectives and concerns about this vaccine is essential in order to ensure optimal uptake rates. Studies on parental attitudes and intention-to-vaccinate have shown that despite the outstanding clinical efficacy and reassuring side-effect profile of this vaccine, concerns remain about the vaccine and about the willingness of parents to have their daughters receive HPV vaccination [9]–[18]. In a recent systematic review on the topic, global HPV vaccine acceptability among parents ranged from 54.9% to 81.0% [19], and studies have highlighted issues such as vaccine safety, impact on sexual practices, age of daughter, awareness of HPV, education, and cervical cancer screening history among many others as key predictors of HPV vaccine acceptance. However, most studies have primarily focused on factors predicting parental intention to have a daughter receive the HPV vaccines and were conducted prior to the approval of the HPV vaccine or implementation of a publicly funded vaccine program. In contrast, data on factors influencing parental decisions for actual or real HPV vaccine receipt in publicly funded and delivered vaccine programs for girls is limited [20]. As publicly funded HPV vaccines programs are now being planned it is critical that parental factors associated with actual uptake of the HPV vaccine are understood.

In Canada, health falls under provincial/territorial jurisdiction and by September 2009, all of the 14 provinces and territories in Canada commenced a school-based HPV vaccine program. In September 2008, the province of British Columbia in Canada embarked on a voluntary, school-based HPV vaccination program for girls in grade 6 (aged 11 y) and grade 9 (aged 14 y) with Gardasil. With the implementation of this program, and given the critical role of parents in vaccine uptake and previous research that indicated that British Columbians were less likely than Atlantic Canadians to intend to have their daughters receive the HPV vaccine [14], we took the opportunity to conduct a population-based evaluation of the HPV vaccine program in the province. We conducted a telephone survey of a random selection of parents of grade 6 girls in the province who were eligible to receive the HPV vaccine. The objective of this evaluation was to assess the level of uptake of the first dose of the HPV vaccine and to determine the factors associated with receipt of the HPV vaccine.

## Methods

### Participants and Data Collection

All parents of girls enrolled in grade 6 during the academic year of September 2008–June 2009 in the province of British Columbia were eligible to participate. Telephone numbers of eligible households were identified through the integrated Public Health information system (iPHIS) program. iPHIS is a software and public health information system used by 14 of 16 Health Service Delivery Areas of British Columbia for notifiable disease reporting, as an immunization registry, and for vaccine-associated adverse event reporting. iPHIS contains identifiers of all individuals who have received a public health service, including well baby examination, hearing and vision screening, and immunization services. Phone numbers of households with a girl in grade 6 in the province were identified as part of a comprehensive HPV vaccine program evaluation, and households were randomly selected to be contacted by telephone after the first dose of the HPV vaccine had been offered through the school-based program and invited to participate in this survey. Parents who consented were interviewed by trained, experienced research staff. The evaluation received ethical approval from University of British Columbia and funding from the BC Centre for Disease Control.

### HPV Vaccine Program in British Columbia

In British Columbia, all vaccines provided in schools, including the HPV vaccine, are fully funded by the public health program in the province. The vaccines are delivered as part of a comprehensive school-based vaccination program for hepatitis B, meningococcal C, tetanus-diphtheria, and acellular pertussis booster, as well as a catch-up program for varicella zoster virus vaccine. In 2008, Gardasil was added to the school-based vaccine program in British Columbia. Trained public health nurses offer these vaccines in all public and independent schools through the entire province free of cost, and in the grade 6 program, parents provide consent for



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their daughters to receive, or not receive, HPV and other vaccines. Children who are absent are able to receive vaccines on days when the school nurses return for other classes, or can attend local public health units to receive the vaccine free of charge. Education for the HPV vaccine program focused on cervical cancer prevention, and was widely promoted through the schools with information packages and DVDs aimed at parents and children. Public health nurses offered local educational sessions where possible. Parents were also provided with the link to [www.immunizeBC.ca](http://www.immunizeBC.ca), which has extensive information on all vaccines, including HPV.

**Theoretical Model**

The survey tool is based on the theoretical model of Theory of Planned Behaviour (TPB) [21]. This psychological model of behaviour change examines how human action is guided and distils the elements that contribute to an actual behaviour (in this case, consent to have a daughter receive the HPV vaccine), or the most proximate measure of change, behaviour intention. According to TPB, behaviours or behavioural intentions are a result of attitudes, subjective norms, and perceived behavioural control. This well-established model provides a foundation for questionnaire development regarding health behaviours or behaviour intentions. For this survey, we will examine the actual behaviour (receipt of the vaccine) and discern parental factors that predict vaccine uptake.

**Survey Instrument Development**

Questionnaire development adhered to the steps needed to construct a TPB questionnaire and was based on a previous study on intention to vaccinate [14]. The “population of interest” was defined as parents of daughters in grade 6 in British Columbia, and the “behaviour under examination” was parental consent (or not) to have daughters receive the HPV vaccine. Behaviour was measured by parental self-report as to whether or not they had consented to have their daughter receive the HPV vaccine. Perceived advantages and disadvantages of the HPV vaccine, most important people/groups who would approve or disapprove of the vaccine, and perceived barriers/facilitating factors were identified through a comprehensive literature search, an elicitation survey of ten parents to determine factors influential in their decision to immunize or not to immunize their daughter(s) against HPV, and results from intention to vaccinate studies [14]. A draft survey including all constructs was pilot tested with parents to ensure comprehension and to ensure no domains of relevance had been missed. Parents identified questions on “barriers/facilitating factors” for this vaccine program that were redundant and confusing, as this was a publicly funded, provincial program delivered at every school by school nurses, thus removing any expected barriers such as cost and access to the program/practitioners.

**Survey Content**

Demographics items assessed included age and gender of respondent, region of residence, age(s) and number of daughters, respondent education, cultural background, history of abnormal Pap smears or cervical cancer, religious affiliation, and family composition. Participants were asked about adherence to childhood vaccination schedules and knowledge of cervical cancer and HPV at the start of the survey. Participants were next asked to report whether or not their daughter had received the hepatitis B, meningococcal C, and HPV vaccine that year, as well as the number of doses of the HPV vaccine received, and intention to complete the series for the HPV vaccine. Parents were asked to provide the main reason for electing to have their daughter receive or not receive the HPV vaccine, as well as any reason for their choice, and these reasons were categorized. Participants were asked about specific psychological constructs that could influence their decision to vaccinate or not vaccinate their daughter with the HPV vaccine. In keeping with TPB, these constructs included attitudes toward vaccines in general and the HPV vaccine in particular, perceived impact of the HPV vaccine on their daughter's sexual practices, and the seriousness of HPV infection and cervical cancer as diseases. These constructs were assessed using seven-point Likert scales (1, strongly disagree; 4, neutral; 7, strongly agree) with four or five items per construct.

**Sampling Frame and Telephone Recruitment**

British Columbia is the most western province of Canada, with a population of more than 4 million. It is divided into five geographic health authorities and each health authority is divided into health service delivery areas (HSDAs). There are a total of 16 HSDAs in the province, and each health authority has either three or four HSDAs. Two of the HSDAs, which include ~15% of the eligible girls in the province, do not use iPHIS, the provincial immunization registry, as their public health information system and thus were not included in the sampling frame. In order to ensure a representative sample from across the province, we generated a sampling frame from British Columbia population estimates for each of the five geographic health authorities of 11-y-old girls for 2008 from Population Extrapolation for Organization Planning with Less Error, run cycle 32 (P.E.O.P.L.E. 32) [22], excluding the two HSDAs not participating. P.E.O.P.L.E. 32 is the subprovincial (local health authority, health region, regional district, and development region) population projections that are released annually by the BC government (BC Stats). P.E.O.P.L.E. 32 was released in 2007. Assuming a population of 20,000 girls in the eligible age cohort, response rate of 50%, and a 95% confidence interval (CI) of  $\pm 2\%$ , we needed to recruit 2,144 participants [23]. We randomly selected participants from the datasets from each health authority, to ensure that at the end of the evaluation we had a representative sample based on the population size of 11-y-old girls in each health authority in the province.



Telephone calls for the evaluation were conducted by an experienced research company who had carried out previous parental attitudinal surveys in British Columbia. Participants were randomly selected from each health authority, and households were contacted in the random order provided. Households were called a maximum of four times, with attempts to contact made in the morning, afternoon, evening, and Saturdays. We stopped calling households once one of the following occurred: participant declined; number not in service; no answer after four attempts; messages left four times; or survey not completed/ineligible.

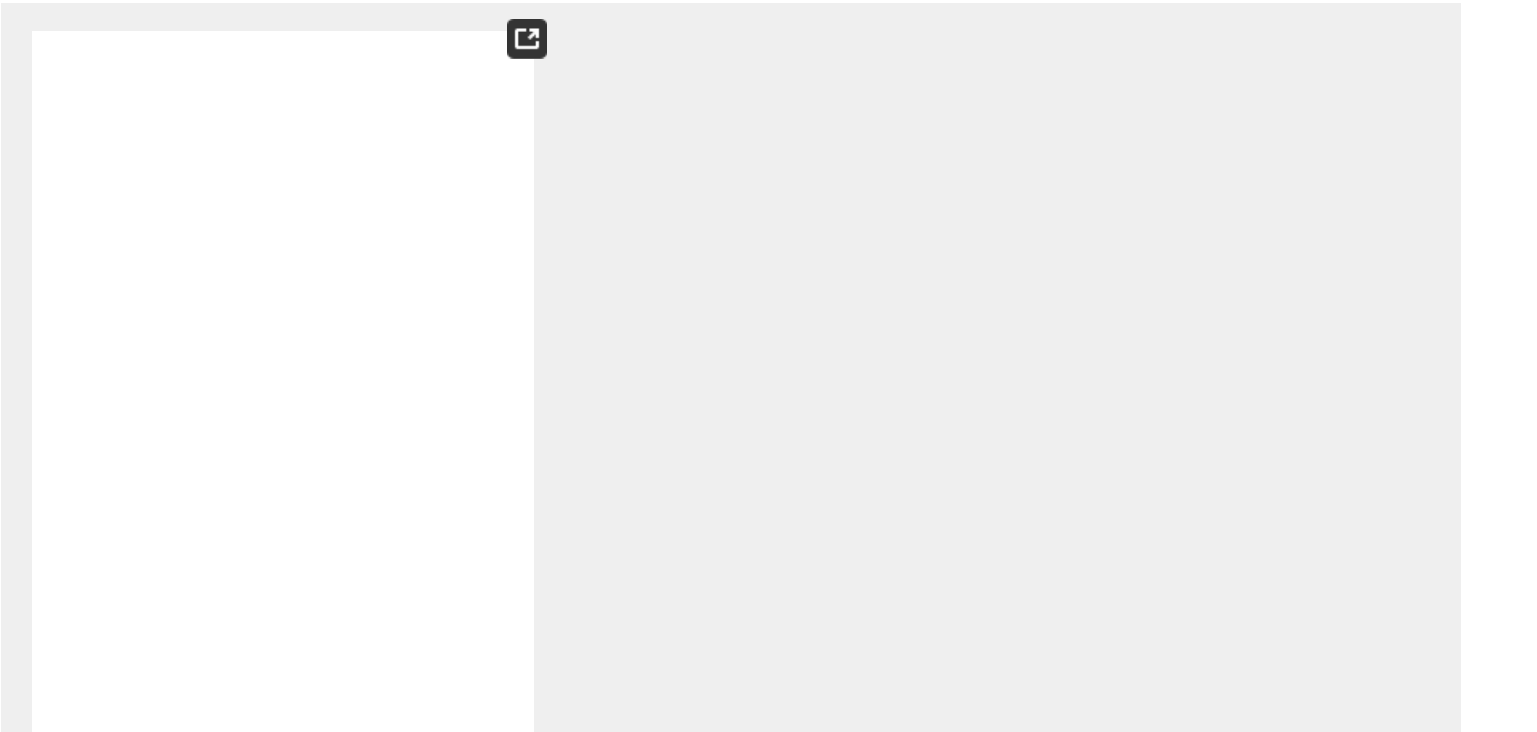
Analysis

Descriptive analyses of sample demographics were conducted. Item reliability was established for psychological construct scales using Cronbach's alpha, and mean values for each scale were calculated. For scale items, composite scale scores were calculated and dichotomized with a mean value of 4.5 as a cut-off, with scores  $\geq 4.5$  indicating a general positive value for the HPV vaccine (i.e., a positive attitude to vaccines, belief that the HPV vaccine had limited influence on sexual behaviour). Composite variables were created for the predictor variables and dichotomized, and then entered into the model as described in the methods. Bivariate analyses were conducted using Chi-square comparing the responses of parents who vaccinated their daughter(s) against HPV to those who did not vaccinate. Variables that achieved  $p < 0.05$  were offered for inclusion in a multivariable model to achieve a best fit model. Logistic regression was conducted to calculate adjusted odds ratios to identify the factors that were associated with parents' decision to vaccinate their daughter(s) against HPV. Backwards logistic regression analysis was conducted to calculate adjusted odds ratios to identify the factors that were associated with parents' decision to vaccinate their daughter(s) against HPV. We also used additional backwards and forward variable selection techniques to confirm that the model and findings were robust (unpublished data). Analyses were conducted with SPSS version 14.0 for Windows.

Results

This program evaluation was carried out between January 18, 2009, and March 19, 2009, 4 mo after the provincial HPV vaccine program commenced. Of the 23,614 girls in grade 6 in the province of British Columbia, contact information was available for 20,161 from 14 of 16 health service areas (85.4%) in iPHIS. 5,489 of 20,161 eligible households, stratified by health authority, were randomly contacted by the research team. Of the 4,335 numbers in service (78.9%), 304 did not speak English. Of the remaining 4,031 eligible to complete the survey, 2,025 parents agreed to complete the survey (50.2%).

Demographic characteristics of the participants are shown on [Table 1](#). The majority of survey respondents were female (84.9%), most had given their daughters all childhood vaccinations (94.1%), and more than 90% had heard of HPV. Respondents were representative of the population distribution of grade 6 girls in health authorities in the province, and 1,318 (65.1%; 95% CI 63.1–67.1) of parents in the survey reported that their daughters had received the first dose of the HPV vaccine. In the same school-based vaccine program, 1,790 (88.4%; 95% CI 87.1–89.7) reported consenting to the hepatitis B vaccine, and 1,751 (86.5%; 95% CI 85.1–87.9) consented to the meningitis C vaccine. In those who received the first dose of the HPV vaccine, 97.5% said that they planned to have their daughter receive the next dose of the HPV vaccine. Of the 34.9% of parents who did not consent to have daughters receive the HPV vaccine, almost 50% stated that they would prefer to have their daughter receive the HPV vaccine in the future.



Characteristics of Respondents (n=2,023)	n (%)
<b>Respondents' gender</b>	
Female	1,719 (84.9)
Male	301 (14.9)
No response	5 (0.2)
<b>Age of respondents (y)</b>	
15–29	17 (0.8)
30–39	632 (31.2)
40–49	1,135 (56.0)
50–59	189 (9.3)
60+	15 (0.7)
No response	37 (1.8)
<b>Child received all childhood vaccines</b>	
Yes (all)	1,903 (94.1)
Yes (some)	82 (4.1)
Unsure	8 (0.4)
No	30 (1.5)
<b>Ever heard of HPV</b>	
Yes	1,878 (92.7)
No	147 (7.3)
<b>History of cervical cancer (self or partner)</b>	
Yes	80 (4.0)
No	1,906 (94.1)
Unsure/missing	39 (1.9)
<b>History of abnormal Pap smear (self or partner)</b>	
Yes	700 (34.6)
No	1,274 (62.9)
Unsure/missing	51 (2.5)
<b>Education</b>	
High school education/vocational school	713 (35.3)
Some or complete undergraduate degree	1,119 (55.3)
Postgraduate degree	156 (7.7)
Missing	37 (1.8)
<b>Family composition</b>	
Single parent/guardian	252 (12.4)
Two parents (male/female)	1,513 (74.7)
Parents/guardians extended family	92 (4.5)
Blended families	128 (6.3)
Missing	40 (2.0)
<b>Number of children</b>	
One or two children	1,297 (64.0)
Three or more children	728 (36.0)
<b>Country of birth</b>	
Canada	1,544 (76.2)
England	54 (2.7)
China	15 (0.7)
India	64 (3.2)
Philippines	39 (1.9)
United States	47 (2.3)
Germany	16 (0.8)
Other	246 (12.1)
<b>Religious background</b>	
Christian (Catholic or Protestant)	327 (16.2)
Christian (other)	440 (21.7)
Sikh	47 (2.3)
Muslim	18 (0.9)
Buddhist	12 (0.6)
Evangelical Christian	8 (0.3)
Jewish	3 (0.1)
Other religion (including other Christian denominations)	476 (23.5)
None	694 (34.3)
<b>Organized religion</b>	
No religious affiliation	632 (31.2)
Religious affiliation	1,393 (68.8)

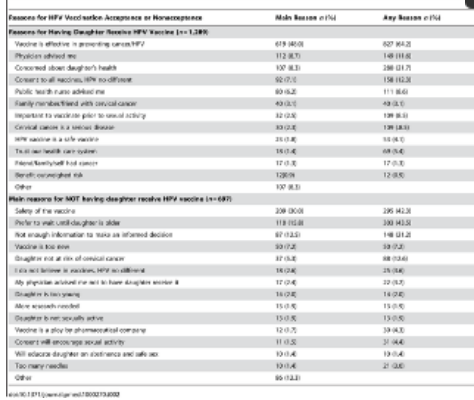
doi:10.1371/journal.pmed.1000270.t001

Table 1. Demographic characteristics of survey respondents.

<https://doi.org/10.1371/journal.pmed.1000270.t001>

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Parents were asked to list both a main (single) reason and any reason for their vaccine choice. The main reasons for having a daughter receive the HPV vaccine were the effectiveness of the vaccine (48.0%), advice from a physician (8.7%), and concerns about their daughter's health (8.3%) (Table 2). The main reasons for not having a daughter receive the HPV vaccine were concerns about HPV vaccine safety (30.0%), preference to wait until the daughter is older (15.8%), and not enough information to make an informed decision (12.5%). For those parents who indicated that they preferred to have their daughter wait as either their main or one of their reasons ( $n=337$ ), more than 46.3% said that they felt they needed more safety data, and 27.0% felt that their daughter was not at risk of sexual activity in grade 6 but might be when they were older.

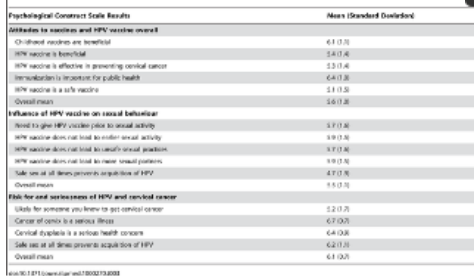


Reasons for Having Daughters Receive HPV Vaccine (n=1,288)	Main Reason n (%)	Any Reason n (%)
Vaccine is effective in preventing cervical cancer	619 (48.0)	627 (49.0)
Physician advised me	112 (8.7)	148 (11.6)
Concerned about daughter's health	107 (8.3)	288 (22.7)
Concern about vaccine side effects	86 (6.7)	188 (14.6)
Public health status address me	80 (6.2)	111 (8.6)
Family member/friend with cervical cancer	49 (3.8)	49 (3.8)
Inspected the vaccine prior to use of school	42 (3.3)	108 (8.4)
Cervical cancer is a serious disease	40 (3.1)	109 (8.5)
HPV vaccine is a safe vaccine	25 (1.9)	10 (0.8)
Trust in health care system	16 (1.2)	68 (5.3)
Family member/friend cancer	17 (1.3)	17 (1.3)
Specific concern about risk	1 (0.1)	12 (0.9)
Other	107 (8.3)	
<b>Main reasons for NOT having daughters receive HPV vaccine (n=485)</b>		
Safety of the vaccine	208 (30.0)	208 (42.8)
Wish to wait until daughter is older	118 (19.4)	168 (34.6)
Not enough information to make an informed decision	87 (13.2)	148 (30.5)
Vaccine is too soon	59 (12.2)	59 (12.2)
Daughter not at risk of cervical cancer	37 (7.6)	68 (14.0)
I do not believe in vaccines/HPV is different	18 (3.6)	28 (5.8)
My physician advised me not to have daughter receive it	17 (3.4)	22 (4.5)
Daughter is too young	16 (3.2)	14 (2.9)
More research needed	15 (3.0)	15 (3.0)
Daughter is not sexually active	13 (2.6)	13 (2.6)
Vaccine is a drug for pharmaceutical company	12 (2.5)	19 (4.0)
Concerns about sexual activity	11 (2.2)	31 (6.4)
Will vaccinate daughter on convenience and safety also	10 (2.0)	19 (3.9)
Trust in my health	10 (2.0)	21 (4.3)
Other	85 (13.3)	

**Table 2. Reasons for having daughters receive or not receive HPV vaccine.**

<https://doi.org/10.1371/journal.pmed.1000270.t002>

Internal reliability of the three psychological constructs using Cronbach's alpha were as follows (Table 3): 0.8, overall attitudes to vaccines; 0.7, attitudes of the impact of the HPV vaccine on sexuality; 0.5, seriousness of HPV disease/cervical cancer. In bivariate analysis, age of respondent, country of birth, knowledge of HPV, religious affiliation, history of abnormal Pap smears, and history of cervical cancer were not associated with having a daughter receive the HPV vaccine. Parents with higher levels of education (more than high school diploma/vocational training) were significantly less likely to consent to having their daughter receive the HPV vaccine (63.3% versus 72.9%,  $p<0.01$ ), and parents from non-traditional families (i.e., families not headed by a male and female) were more likely to have their daughters receive the HPV vaccine (71.6% versus 63.1%,  $p<0.01$ ) (Table 4). We did our analysis plan such that variables inputted into the model had to achieve significance in the bivariate model. In multivariate analysis, overall attitudes to vaccines, impact of the HPV vaccine on sexual practices, and childhood vaccine history were predictive of parents having daughter's receive the HPV vaccine in a publicly funded school-based HPV vaccine program. In contrast, having a family with two parents, having three or more children, and having more education was associated with a decreased likelihood of having a daughter receive the HPV vaccine (Table 5).



Psychological Construct Scale Results	Mean (Standard Deviation)
<b>Attitudes to vaccines and HPV vaccine overall</b>	
Childhood vaccines are beneficial	4.1 (0.7)
HPV vaccine is beneficial	3.4 (0.4)
HPV vaccine is effective in preventing cervical cancer	3.3 (0.4)
Recommendations to recommend the public health	3.4 (0.3)
HPV vaccine is a safe vaccine	3.1 (0.3)
Overall mean	3.4 (0.3)
<b>Influence of HPV vaccine on sexual behavior</b>	
Wish to give HPV vaccine prior to sexual activity	3.7 (0.3)
HPV vaccine does not lead to earlier sexual activity	3.9 (0.3)
HPV vaccine does not lead to earlier sexual practices	3.7 (0.3)
HPV vaccine does not lead to more sexual partners	3.9 (0.3)
Safe use of all sexual practices regardless of HPV	3.7 (0.3)
Overall mean	3.7 (0.3)
<b>Risk for and seriousness of HPV and cervical cancer</b>	
Wish for vaccine you know to get cervical cancer	3.2 (0.3)
Cancer of cervix is a serious illness	4.7 (0.5)
Cervical dysplasia is a serious health concern	4.4 (0.6)
Safe use of all sexual practices regardless of HPV	4.2 (0.3)
Overall mean	4.1 (0.3)

**Table 3. Results of psychological construct scales.**

<https://doi.org/10.1371/journal.pmed.1000270.t003>

Characteristics of Respondents	Daughter Received HPV Vaccine n (%)
<b>Respondents' gender</b>	
Female	1,122 (65.3)
Male	192 (63.8)
<b>Age of respondents (y)</b>	
19–29	16 (94.1)
30–39	438 (69.3)
40–49	703 (61.9)
50–59	126 (66.7)
60+	11 (73.3)
<b>Child received all childhood vaccines</b>	
Yes (all)	1,280 (67.3)
Yes (some)	29 (35.4)
Unsure	7 (87.5)
No	1 (3.3)
<b>Ever heard of HPV</b>	
Yes	1,213 (64.6)
No	105 (71.4)
<b>History of cervical cancer (self or partner)</b>	
Yes	61 (76.3)
No	1,231 (64.6)
Unsure/missing	8 (66.6)
<b>History of abnormal Pap smear (self or partner)</b>	
Yes	476 (68.6)
No	807 (63.3)
Unsure/missing	16 (69.6)
<b>Education</b>	
High school/vocational school	493 (69.1)
Some/complete undergraduate degree/college	700 (62.6)
Postgraduate degree	100 (64.1)
<b>Family composition</b>	
Traditional (two parents, male and female)	954 (63.1)
Nontraditional	338 (71.6)
<b>Number of children</b>	
One or two children	878 (67.7)
Three or more children	440 (60.4)
<b>Country of birth</b>	
Canada	999 (64.7)
England	33 (61.1)
China	10 (66.7)
India	50 (78.1)
Philippines	29 (74.4)
United States	29 (61.7)
Germany	11 (68.8)
Other	157 (63.8)
<b>Organized religion</b>	
No religious affiliation	439 (69.5)
Religious affiliation	879 (63.1)

doi:10.1371/journal.pmed.1000270.t004

Table 4. Bivariate analysis of uptake rate of HPV vaccine in population.  
<https://doi.org/10.1371/journal.pmed.1000270.t004>



Factors Associated with HPV Vaccine Uptake	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
<b>Childhood vaccine history</b>		
Received none or no childhood vaccines	1.0	1.0
Received all childhood vaccines	3.9 (2.5-5.9)	1.2 (1.1-2.5)
<b>Education of respondent</b>		
High school/technical school	1.0	1.0
Some college/university degree/diploma	6.7 (3.4-13.0)	3.8 (3.0-5.0)
Postgraduate degree	6.8 (3.4-13.1)	3.8 (3.4-5.0)
<b>Family composition</b>		
Traditional family composition	1.0	1.0
Two-parent family composition	6.7 (3.4-13.0)	3.7 (3.0-5.0)
<b>Number of children</b>		
One or two children	1.0	1.0
Three or more children	6.7 (3.4-13.0)	3.8 (3.0-5.0)
<b>Form of respondent relation</b>		
No religious affiliation	1.0	—
Religious affiliation	6.7 (3.4-13.0)	—
<b>Attitudes to HPV vaccine and vaccines overall</b>		
Negative attitudes to vaccines	1.0	1.0
Positive attitudes to vaccines	12.0 (8.3-18.4)	8.5 (6.1-11.9)
<b>Impact of HPV vaccine on sexual practices</b>		
Negative impact on sexual practices	1.0	1.0
Positive impact on sexual practices	6.8 (3.4-13.0)	5.1 (3.9-6.5)
<b>Encouragement of cervical cancer and HPV disease</b>		
Cervical cancer/HPV disease not serious	1.0	—
Cervical cancer/HPV disease serious	3.9 (2.5-5.9)	—
<b>Receipts of vaccines received with HPV vaccine</b>		
No receipt of vaccine received	1.0	—
Receipts of vaccine received	5.1 (3.4-7.2)	—
<b>Receipts of vaccines received with HPV vaccine</b>		
No receipt of vaccine received	1.0	—
Receipts of vaccine received	5.0 (3.4-7.1)	—

doi:10.1371/journal.pmed.1000270.t005

**Table 5. Multivariate analysis of factors associated with parents' decision to have daughters receive the HPV vaccine in a publicly funded HPV vaccine program.**  
<https://doi.org/10.1371/journal.pmed.1000270.t005>

Discussion

This program evaluation offers important insights into factors that are associated with parental decisions about receipt of the HPV vaccine in pre-adolescent girls in a program where neither the cost of the vaccine nor access to health care are barriers. In this population-based evaluation of a publicly funded, school-based HPV vaccine program for girls aged 11 y in Canada, parents reported that 65.1% of eligible girls received the first dose of the HPV vaccine, compared to reported receipt of 88.4% for the hepatitis B vaccine, and 86.5% for the meningitis C vaccine. Parents cited vaccine efficacy, advice from a physician, and concerns about daughters' health as the main reasons for choosing to have daughters receive the vaccine. In contrast, concerns about vaccine safety, a desire to wait until their daughter was older, and lack of information were main reasons for not having daughters receive the vaccine. In multivariate modeling, overall attitudes to vaccines and the HPV vaccine, limited concern about the influence of the HPV vaccine on sexual behaviour, and receiving childhood vaccines were associated with having a daughter receive the HPV vaccine. In contrast, family composition (two parents), having more children, and higher education were associated with not having a daughter receive the HPV vaccine. Of note, none of the following factors were associated with decisions to receive the HPV vaccine: religious affiliation, country of birth, or a self-reported history of abnormal Pap smears or cervical cancer.

In a previous study [14], parental intention to have daughters receive the HPV vaccine in British Columbia was 62.8% (95% CI 60.2–65.4), which approximates both the reported parental uptake in this current study at 65.1% and first dose HPV vaccine uptake reported in the provincial clinical immunization record in the province for 2008 of 64.8% [24]. This finding indicates that intention to vaccinate studies can be very useful in planning for actual uptake of the HPV vaccine, albeit with limitations. Comparing the intention to vaccinate [14] with our study, some common factors emerge as key predictors of intention to vaccinate and actual vaccination. These factors included overall attitudes to vaccines and role of the HPV vaccine on sexual behaviour. In our study of actual HPV vaccine uptake, previous actions around vaccines, including childhood vaccine history, were positively associated with the decision to have daughters receive the HPV vaccine. A higher level of parental education and more traditional family composition, including greater numbers of children and two-parent families, were associated with a decision to not have daughters receive the vaccine. These factors were not evident in the intention to vaccinate survey, underscoring the importance of examining actual rather than intended behaviour.

This evaluation has important implications broadly for HPV vaccine policy, because there were neither financial nor organizational barriers to receipt of the HPV vaccine in this program. The vaccine program was fully funded for all girls in grade 6 and was delivered in schools throughout British Columbia as part of a well-established school-based immunization program. Despite this access to the program, almost 35% of parents elected not to have their daughters receive the HPV vaccine. In an examination of parents of almost 3,000 girls aged 12 and 13 y in Manchester, United Kingdom, vaccine uptake was 70.6% for the first dose [20], and parents identified vaccine safety and long term data as a key factor in vaccine refusal. In a qualitative study of 52 parents, Dempsey et al. found that parents identified lack of knowledge, safety, and a perception that their daughter was too young as factors associated with declining of the HPV vaccine [25]. In a study of 153 mothers that included both those intending to have daughters vaccinated and those who had vaccinated their daughters, less education, parental history of a sexually transmitted infection, parental supervision, and acceptance of the vaccine schedule were associated with HPV vaccine acceptance [26]. The findings of these studies echo those found in this study in which parents expressed concerns about the long term safety of the HPV vaccine as a primary reason for refusing to have daughters vaccinated. Parents who did not permit their daughters to receive the vaccine were also concerned about the young age of their daughters, believed the vaccine condoned sexual activity, or believed their daughter was at low risk for acquiring HPV. It is noteworthy that in British Columbia, prior to implementation of the HPV vaccine program, one of the most comprehensive vaccine education programs to date for the province was implemented. These efforts targeted issues such as vaccine safety and efficacy and were delivered in several user-friendly formats including the [www.immunizeBC.ca](http://www.immunizeBC.ca) Web site, through DVDs targeted at parents and girls, as well as with pamphlets and brochures and locally

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held information sessions for parents and providers. In addition, this vaccine was strongly recommended by several independent expert health groups, such as the Canadian National Advisory Committee on Immunizations [27]. However, despite these efforts, many parents still perceived that information was inadequate for them to make an informed decision about HPV vaccination.

In keeping with the findings of two recent studies, this evaluation noted that parents with more education were less likely to consent to their daughters receiving the HPV vaccine [17],[26]. This is a surprising outcome, and in contrast to most studies on vaccine rates in children and maternal education, where higher maternal education is associated with higher childhood vaccine rates [28]. There are several differences to consider as we compare our findings to existing literature. The HPV vaccine program in British Columbia is delivered in optimal conditions with limited barriers, and so several of the issues that may cause lower uptake rates in less-educated parents in other jurisdictions may not be operating for this program. Specifically, the HPV vaccine program in British Columbia is part of a well-established adolescent school-based vaccine program, where vaccines are offered at school, during school hours, by trained health professionals. As a result, parents do not need to get prescriptions, leave work, or arrange to bring children to an office or clinic to receive the vaccine. Parents do not need to pay for the vaccine, so there are no financial constraints for parents. Nurses return to schools several times so that children have the opportunities on other occasions to receive their vaccinations. Our evaluation examined uptake of vaccines in an adolescent as opposed to infant/toddler population, so some of the previous findings and underpinning barriers for infants/toddlers may not be as relevant. This evaluation also examined a newly launched as opposed to a well-established vaccine, and so the factors operating in parental decision making may also be different.

Literature has noted that, in settings with low childhood vaccine uptake rates in less-educated mothers, programmatic structures can reduce the impact of maternal education on vaccine uptake rates. In a recent review by Racine [28], higher maternal education, independent of income and race/ethnicity, was associated with higher child immunization rates. He found, however, that in jurisdictions where there were greater subsidies for childhood vaccines, there was a significantly smaller difference between rates of immunization in children of less versus more educated mothers. This analysis of US data proposed that with increased public funding for vaccines, many of the barriers that create the immunization rate gradient, such as price and availability, decline in their importance, and the advantages offered by maternal education with respect to childhood vaccine receipt are attenuated. In a setting such as British Columbia, where there are even more programmatic advantages such as offering the vaccine in the school setting, the factors that lead to lower uptake rates in less-educated parents in other settings may be diminished by the organization of the adolescent immunization program in the province.

Further research and examination is needed to understand this unique relationship. In a recent qualitative study on Texan parents who opt out of childhood vaccine programs, Gullion et al. noted that the parents were highly educated and reported very sophisticated data collection and information processing from a variety of sources including online sources [29]. Educated parents are often more likely to have access to the Internet and other forms of media compared with less-educated parents in the province, and may feel more comfortable researching the Internet for vaccine information. This research may increase access to some of the Web sites that provide contradictory and potentially inaccurate information about the HPV vaccine and increase parents' concerns about vaccine risks. Highly educated parents may also perceive that they are able to interpret complex scientific and clinical health information and trials independently without the assistance of practitioners. In Gullion's work, parents reported high distrust of the medical community and felt that they were better equipped to conduct research on vaccines and more knowledgeable than the medical practitioners on the topic of vaccines [29]. Educated parents may also have felt more comfortable delaying their daughters' vaccination beyond aged 12 y as they would be able to purchase the vaccine privately in the future, should they choose to do so. Guillon's study noted that parents often felt rushed regarding decisions around vaccines, and so the perceived opportunities for discussion about the attributes and risks of vaccines were limited. Clearly, there is a need for further exploration of this topic to understand why educated parents chose to decline the HPV vaccine for their daughters. As educated parents can often be opinion leaders within their communities and school groups, it is particularly important to consider ways to ensure that these parents have accurate information about this and other vaccines, and appropriately contextualize vaccine risk and safety with the risks and sequelae of the vaccine-preventable disease.

Parents who were concerned about the potential impact of the HPV vaccine on sexual practices were less likely to have their daughters receive the HPV vaccine. Over the past 10 y, British Columbia has had a hepatitis B vaccine program for 11-y-old girls and boys. In the corresponding time period, the Canadian provincial adolescent health survey has reported an improvement in sexual practices in adolescents, with delayed sexual debut, as well as safer sexual practices, despite the availability of a vaccine for a sexually transmitted infection in a publicly funded school program in the province [30]. It will be critical to ensure that parents are aware that provincial data have shown that the use of a vaccine for a sexually transmitted infection does not increase risky sexual behaviour.

The goal of this evaluation was to inform, in real time, vaccine promotion efforts in the province of British Columbia to ensure that educational efforts responded to the concerns of the population. From this survey, it is clear that messaging should continue to focus on the effectiveness of the HPV vaccine, and continue to highlight the established safety of the HPV vaccine, as well as the importance and safety of vaccines in general. Health professionals remain central in influencing parents' decision around the HPV vaccine, and education should also target physicians and nurses to ensure that they also possess accurate information for parents who seek their council. Parents need to be aware that the use of a vaccine for a sexually transmitted infection (hepatitis B) over the past 10 y in British Columbia has not adversely affected the sexual health of adolescents [30]. In contrast, during this same time period, they appear to be making better sexual health decisions.



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Limitations of this study include our inability to access parents in two health service areas that account for ~15% of the population of the province and the use of a telephone methodology. Although there were quality assurance interviews both at training with a random review of telephone calls by supervisors and individual quality assurance reviews for data entry, participants were not surveyed twice. Telephone surveys are biased towards English speakers, and there were 304 potential households who could not participate in this evaluation because of a language barrier. However, this was not a random digit survey, and we were able to use telephone numbers provided to public health services by parents, so biases towards access to land lines should be greatly diminished. Regardless, the reported HPV vaccine uptake rate in this evaluation mirrored the uptake rate reported through the provincial clinical immunization record in the province of 64.8% [24]. With a population-based, randomly selected sample of over 2,000, representing almost 10% of the eligible population for the program, we expect these findings to be highly generalizable and informative for HPV vaccine policies in high-income countries worldwide.

This study is one of the first population-based assessments of factors associated with HPV vaccine uptake in a publicly funded school-based program worldwide. Policy makers need to consider that even with the removal of financial and health care barriers, parents, who are key decision makers in the uptake of this vaccine, still possess some hesitancy to have their daughters receive the HPV vaccine. As populations become less familiar with the diseases that vaccines prevent and the sequelae of these diseases, there is a greater focus on the adverse events associated with vaccines, without the consideration of the morbidity and mortality associated with the disease itself, nor the burden of disease averted by the vaccine [31]. The experience with the HPV vaccine highlights the continued need to ensure that the public is informed and receives credible and clear information about both the scientific evidence for immunizations, as well as information about adverse events associated with vaccines in context. Use of the news media, including the Internet, is essential for connecting with the population, and policy makers must ensure that information speaks broadly to the overall benefits of vaccines at a population and individual level, as well as highlighting the attributes of particular vaccines.

## Author Contributions

ICMJE criteria for authorship read and met: GO MA FM SM KP MD MM TE SD DM DMP MN. Agree with the manuscript's results and conclusions: GO MA FM SM KP MD MM TE SD DM DMP MN. Designed the experiments/the study: GO MA FM SM KP SD DMP MN. Analyzed the data: GO MA MD. Collected data/did experiments for the study: GO MA TE. Enrolled patients: GO MA MN. Wrote the first draft of the paper: GO. Contributed to the writing of the paper: GO FM SM KP MM TE SD DM DMP MN. Revision of document for important intellectual content, and approval of final version: MD. Reviewed the final version of the paper: SD.

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# **EXHIBIT 281**



## Original article

## Uptake of HPV Vaccine: Demographics, Sexual History and Values, Parenting Style, and Vaccine Attitudes

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## Abstract

**Purpose:** To examine the relationships of demographics, parenting, and vaccine attitudes with the acceptance of the human papillomavirus (HPV) vaccine or to the intent to vaccinate in the next 12 months.

**Methods:** Mothers (n = 153) with daughters ages 11 to 17 years were recruited through the pediatric clinic waiting room/announcements to complete a questionnaire.

**Results:** Eighteen percent of the daughters had not received the vaccine, although it had been offered; 34% had not been offered the vaccine and did not intend to get it in the next 12 months; 22% had not been offered the vaccine but intended to get it in the next 12 months; 26% had started vaccination or completed the series. In a multinomial, multivariable logistic regression model, those mothers who had less than a high school degree, had a history of a sexually transmitted infection, supervised their daughter more when she was with peers, and whose daughter would not mind three shots were more likely to be favorable about their daughter being vaccinated. The following variables were not related to their attitudes about getting the vaccine: mothers' and daughters' ages, race/ethnicity, mothers' self-reported history of HPV disease and age of sexual initiation, daughters' dating status and anticipated age of sexual initiation, the number of sexual topics discussed and level of comfort, mother's sexual values, and the family environment.

**Conclusions:** Mothers' decisions about the HPV vaccine were not related to their sexual values or their daughters' sexual behavior, but rather their parenting, sense of vulnerability, and vaccine attitudes. Mothers who were not planning to vaccinate did not appear to not feel an urgency given the newness of the vaccine, and many planned to vaccinate eventually. © 2008 Society for Adolescent Medicine. All rights reserved.

**Keywords:** HPV; Vaccine; Acceptability; Sexuality; Parenting; Sexually transmitted diseases

There are currently two vaccines for the prevention of human papillomavirus (HPV), one of which has obtained U.S. Food and Drug Administration approval and one of which is in the approval process. On March 12, 2007, The

Advisory Committee on Immunization Practices (ACIP) published its current recommendation, which is that the three-dose HPV vaccine be administered routinely to all females 11 to 12 years of age as well as 13- to 26-year-olds who have not previously received the vaccine. The vaccine is licensed for females as young as 9 to 10, but ACIP has left vaccination of this age group to the provider's discretion [1]. Recommendations for the vaccine may change over time and with the availability of the bivalent vaccine.

Studies conducted prior to approval of the vaccine demonstrated that both parents and pediatricians preferred to

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give this vaccine at older ages [2–7]. However, the ACIP recommendation for universal vaccination starting at ages 11 to 12 years is supported by the high levels of immunological antibody response in young adolescents, the stabilization of titers at levels above those found in natural infection 3 years after immunization, the risk of acquiring HPV shortly after sexual initiation, and the success of age-based versus risk-based strategies [3]. Thus, vaccinating 11- to 12-year-olds would reach adolescents who are still attending well-child/preventive visits, unlikely to be sexually experienced, and likely to be well protected in their later teen or young adult years when they become susceptible through the initiation of intimate sexual behaviors. In addition, it is critical to immunize older teens, even those who are sexually experienced, because they are still likely to be susceptible to some if not all vaccine-preventable types.

Despite hypothetical concerns that parents would be resistant to vaccination because of the sexual transmission of the virus, studies of parental attitudes prelaunch of the vaccine suggested that they had positive attitudes toward HPV vaccination for their adolescents [2]. This is likely, because for most parents their primary concern is protecting their child from harm, and thus, efficacy of the vaccine and severity of the illness are most critical [8,9]. However, the minority of parents who indicated a lack of acceptance of the HPV or sexually transmitted infections (STIs) vaccines described concerns about the risk of sexual disinhibition or the promotion of sexual activity [2–4,8].

There may be other aspects of parenting and experiences that are related to HPV vaccine acceptance. Parenting behaviors are associated with sexual health of adolescents, and thus, may be related to vaccine decision making. Specifically, both communication about sexuality and supervision of their adolescent's whereabouts have been shown to be associated with having adolescents who delay the initiation of sexual intercourse [10–15]. With regard to sexual experiences, previous vaccine acceptability research demonstrated that parents with an STI history and those adolescents with friends who were having intercourse were more accepting of STI vaccines [8]. Therefore, in addition to the traditional predictors of vaccine acceptability such as a healthcare provider's recommendation, the perceived safety of the vaccine, the severity of the illness, and the risk of the infection [3,5,8,9,16–20], it may be that parenting behaviors and attitudes toward sexuality will play an important role in the uptake of the HPV vaccine and future STI vaccines.

Thus, the purpose of the present study was to examine the relationships of demographics of the mother and daughter (ages 11–17 years), parenting behaviors and attitudes, and vaccine attitudes to the acceptance of the HPV vaccine or stated intent to vaccinate in the next 12 months. Mothers whose daughters were 18 years and over were not enrolled, because those young women did not need parental consent to be vaccinated.

## Methods

The participants in this study were mothers, aunts, grandmothers, or other female care providers of adolescent girls (ages 11–17 years) who were patients at a university-based primary care clinic. For simplicity sake, for the remainder of this manuscript, the participants will be referred to as “mothers.” They were recruited through the clinic waiting room or via the university's daily e-mail announcement. Recruitment occurred between April 27, 2007 and January 7, 2008. At the time of data collection, all of the major insurance carriers and Vaccine for Children covered the vaccine. Each mother was paid \$20.00 for her time and transportation.

The self-administered questionnaire was developed based on a review of the literature, previous research experience, and a pilot questionnaire to a convenience sample of 15 mothers. The mothers enrolled in the pilot portion of the study completed the questionnaire and then were interviewed to obtain feedback on the questionnaire. These mothers were given \$30.00 for their time and transportation because these study visits took longer than merely filling out the questionnaire. Based on the pilot data, minor changes were made to those items that were not part of a preexisting standardized measure such as the Family Environment Scale (FES) [21].

Each mother was asked to provide demographic information about herself, including her relationship to her daughter, age, race/ethnicity, highest level of education, age of sexual initiation, history of STI (which could have included HPV) and history of genital warts, cervical dysplasia, or abnormal pap smear. For purposes of analysis, the mother's answers to those three questions were combined to indicate any possible self-reported history of HPV disease. She also reported on her adolescent daughter's age, whether her daughter had started dating, and whether the mother anticipated sexual initiation by the end of high school.

Aspects of parenting that were assessed included supervision, family environment, and communication. Three types of parental monitoring (direct, direct when with peers, and indirect) were assessed [2]. Direct monitoring is related to the mother's actual physical presence with the adolescent and indirect monitoring is related to the mother's knowledge of the whereabouts of the adolescent. These were four-point scales with a score of 1 on the direct monitoring scale corresponding to the adolescent never being without adult supervision, and a score of 4 corresponding to the daughter being unsupervised from 11 or more hours a week. On the indirect monitoring scale a score of 4 indicates that the mother “always” knows where her daughter is and with whom she is with, and a score of 1 indicates that the mother “never” knows. This scale has been shown to be related to use of dual contraception, timing of sexual initiation, and adolescents communication with their mother about participation in a research study [22–24]. Family environment was measured by the relationship dimensions (cohesion,

expressiveness, conflict), the system maintenance dimensions (organization, and control) and one subscale from the personal growth dimension (moral–religious emphasis) of the FES [21]. The *t*-scores (mean of 50; standard deviation of 10) are derived from raw scores for each subscale. Prior research has shown that higher scores on the moral–religious subscale based on the adolescents’ report were related to adolescent girls having an older age of sexual initiation [23]. With regard to communication, mothers were asked (yes/no) if they had talked about eight sexual topics (period, protecting herself against STD/AIDS, condoms, birth control, dating and romantic relationships, making decisions about sex, pregnancy, and her friends’ sexual behaviors) with their daughters. The eight items were summed to create a score of the total number of sexual topics discussed [25,26]. The mothers also were asked to respond to five questions that rated, on a five-point Likert scale, their agreement with statements assessing their comfort in discussing sexuality with their daughters [25,27], for which a mean score was calculated. A high score means agreement with the following statements regarding conversations about sex: I don’t know enough; it would embarrass my daughter; it would be difficult; my daughter will get the information elsewhere so I don’t need to; talking to my daughter will encourage her to have sex. In addition, mothers were asked to choose the statement that best described their sexual values for their adolescents. The options were: shouldn’t have sexual intercourse until she is married, shouldn’t have sexual intercourse until she is in a serious relationship and a young adult, shouldn’t have sexual intercourse until she is in a serious relationship, and should explore her sexuality when she is ready as long as she takes care of herself.

The mothers rated seven health beliefs regarding vaccination and HPV infection on a Likert scale, perceptions of disease severity, susceptibility, and barriers to vaccination, such as the vaccine being too expensive. These items were drawn from previous experience with surveys on vaccine acceptability [5,6,18,20,28,29].

Finally, each mother was asked whether the healthcare provider had offered HPV vaccine for her daughter, and if so, whether her daughter had been vaccinated. Mothers were asked to describe the reasons behind their vaccination decisions. If her daughter had not gotten the vaccine, each mother was asked whether she intended to get her daughter vaccinated in the next 12 months. These answers were divided into four levels of outcomes: had been offered the vaccine and not gotten it regardless of intent, had not been offered the vaccine and did not intend to get it in the next 12 months, had not been offered the vaccine yet and intended to get it in the next 12 months, started or completed the series.

The predictors were tested in logistic regression analyses. Those predictors that were significant at the  $p < .10$  were then included in a multinomial, multivariable logistic

regression model. In this model, the four outcome categories were treated as an ordinal variable, with mothers who were offered, but refused the vaccine defining the low end and mothers who had started their daughters with the vaccine at the high end. In an ordinal logistic regression model, each outcome category is compared to the previous outcome category (e.g., mothers who had been offered the vaccine and not gotten it regardless of intent vs. those who had not been offered the vaccine and did not intend to get it in the next 12 months) under the proportional odds assumption. The variable selection strategy of backward elimination was implemented to choose a final model, with  $\alpha = .05$ . With regard to the qualitative data, the mothers’ reasons for vaccinating or not vaccinating were sorted into word files based on thematic content.

## Results

### Recruitment

One hundred fifty-four mothers completed the questionnaire. The research coordinator approached 170 women in the clinic waiting room, of who 140 met eligibility requirements. Reasons for nonparticipation included lack of time or interest, non-English speaking, or concerns about research participation. A total of 116 completed the questionnaire (response rate from the clinic = 83%). E-mail announcements ran six times from September 21 to November 8, 2007, and 38 participants were recruited in this manner. The response rate was not able to be determined from this method of recruiting. One questionnaire was deemed unusable because of the amount of missing or unusable data. Thus, the final sample size was 153. There was no difference in the outcome measure based on location of recruitment.

### Participants

Most participants were mothers (89%), and the participants had a mean age of 41 years (range = 27–77 years). The sample was 39% African American, 34% non-Hispanic Caucasian, 20% Hispanic, and 7% other. The remainder of the demographics and sexual history variables are presented in Table 1.

Specific means and percentages for the mothers’ parenting and sexual values are presented in Table 2. The mothers reported that their daughters were rarely alone without a parent and when they were, the mother almost always knew where they were and with whom. The FES subscale scores ranged from a low of 45 for the cohesion subscale and a high of 52 for both the organization and moral–religious subscales. Most mothers discussed many sexual topics with their daughters and disagreed with statements suggesting that they were uncomfortable to talk about sex with their daughters. Half of the mothers reported that they thought their daughters should wait until they were married to have sexual intercourse.

The mothers rated on a five-point Likert-type scale their agreement with a series of seven health belief statements



Table 1

Descriptive statistics of mothers and daughters demographic and sexual history (N = 150–153)

Variable	Mean (SD)	Percentage
Mothers' education		
≤High school		22%
>High school		78%
Mothers' age of sexual initiation		
≤14 years		12%
15–17 years		40%
>18 years		48%
Mothers' STI history		
No		83%
Yes		17%
Mothers' history of HPV disease		
No		63%
Yes		37%
Daughters' age	14.0 (1.8)	
Daughters' dating status		
Never dated		84%
Dated		16%
Daughters' anticipated age of sexual initiation		
Not before end of high school		33%
Yes, before the end of high school		21%
Not sure		46%

STI = sexually transmitted infection; HPV = human papillomavirus.

regarding vaccination and HPV infection (Table 3). For purposes of analyses, two of these statements were reversed scored, so that all of the statements went in the direction of having positive attitudes toward vaccines. In general, these mothers had positive attitudes toward vaccination, and only a perception that the daughter might be at future risk for HPV and that the daughter would not mind getting three shots had enough variance to be used as predictors. It should

Table 2

Descriptive statistics of parenting and sexual values (N = 149–153)

Variable	Mean (SD)	Percentage
Direct monitoring	1.9 (0.7)	
Direct monitoring with peers	1.6 (0.6)	
Indirect monitoring	3.7 (0.6)	
Number of sexual topics discussed	6.4 (2.4)	
Comfort with sexual conversations	1.7 (0.6)	
FES cohesion	45.9 (9.2)	
FES expression	46.9 (9.6)	
FES conflict	48.8 (7.0)	
FES moral/religious	52.4 (7.1)	
FES organization	48.2 (8.3)	
FES control	52.3 (7.5)	
Mother's sexual values		
Wait until married		50%
Wait until serious relationship and young adult		36%
Wait until serious relationship; explore her sexuality		14%

FES = family environment scale.

Table 3

Percentage of mothers responding to health beliefs statements regarding vaccination and HPV infection (N = 150–153)

Health belief statements	Percentage
I don't like giving my daughter any vaccines	
Strongly disagree/disagree	69%
Neither agree or disagree	20%
Strongly agree/agree	11%
The HPV vaccine will be too expensive	
Strongly disagree/disagree	44%
Neither agree or disagree	47%
Strongly agree/agree	9%
The HPV vaccine can protect my daughter against cervical cancer and warts	
Strongly disagree/disagree	7%
Neither agree or disagree	18%
Strongly agree/agree	75%
My daughter is at risk for HPV in the future	
Strongly disagree/disagree	18%
Neither agree or disagree	29%
Strongly agree/agree	53%
Getting infected with the HPV virus may lead to very serious illnesses such as cervical cancer	
Strongly disagree/disagree	13%
Neither agree or disagree	10%
Strongly agree/agree	77%
My daughter will not mind getting three shots over a 6-month period	
Strongly disagree/disagree	30%
Neither agree or disagree	25%
Strongly agree/agree	45%
The HPV vaccine will be safe for my daughter to get	
Strongly disagree/disagree	10%
Neither agree or disagree	33%
Strongly agree/agree	57%

HPV = human papillomavirus.

be noted that none of the mothers who had vaccinated their daughters viewed the vaccine as unsafe.

Twenty-seven (18%) of the mothers had been offered the vaccine, but had not had their daughters vaccinated; 52 (34%) had not been offered vaccine and did not intend to get it in the next 12 months; 34 (22%) had not been offered vaccine yet, but intended to get it in the next 12 months; 40 (26%) had started or completed the series.

#### Prediction of vaccine intent/uptake

All of the predictors were tested for significance using ordinal logistic regression analysis (Table 4). Those that were significant at the  $p < .10$  were included in a final multivariable logistic regression model. In the individual analyses, the following were significant predictors (at  $p < .1$ ): mother's level of education,  $\chi^2(1) = 4.1$ ,  $p < .04$ , mother's history of STI,  $\chi^2(1) = 7.5$ ,  $p < 0.01$ , direct monitoring with peers, Wald  $\chi^2(1) = 7.1$ ,  $p < 0.01$ , indirect monitoring, Wald  $\chi^2(1) = 2.9$ ,  $p < 0.09$ , and the daughter not minding three shots,  $\chi^2(1) = 14.2$ ,  $p < 0.01$ . When these predictors were all entered into the multinomial, multivariable logistic regression model using backward



Table 4  
Multivariate analyses of factors associated with uptake of the HPV vaccine

Factors	Odds ratios (95% CI)	
	Unadjusted	Adjusted <sup>a</sup>
Mother		
Education		
>High school <sup>b</sup>	1	1
≤High school	1.4 (1.0, 2.0)	1.4 (1.0, 2.0)
STI history		
No <sup>b</sup>	1	1
Yes	3.3 (1.4, 5.0)	3.4 (1.5, 7.9)
Parenting		
Greater indirect monitoring	1.6 (0.9, 2.7)	—
Greater direct monitoring w/peers	2.0 (1.1, 3.3)	2.5 (1.7, 5.0)
Health belief statements		
Not mind three shots	2.0 (1.4, 2.5)	1.9 (1.3, 2.8)

CI = confidence interval; STI = sexually transmitted infection.

<sup>a</sup> All factors listed in the table were tested in ordinal, multivariable logistic regression.

<sup>b</sup> Reference category.

elimination, the following remained significant at the  $p < .05$  level: mother's education, Wald  $\chi^2(1) = 3.9$ ,  $p = 0.05$ , mother's history of an STI, Wald  $\chi^2(1) = 8.2$ ,  $p < 0.01$ , direct monitoring with peers, Wald  $\chi^2(1) = 14.0$ ,  $p < 0.01$ , and the daughter not minding three shots, Wald  $\chi^2(1) = 12.5$ ,  $p < 0.01$ . Those mothers who had no more than a high school education, had an STI history, who monitored their daughters more when with peers, and whose daughters would not mind three shots were more likely to be favorable about their daughters getting the HPV vaccine (Table 4). The following variables were not related to their attitudes about getting the vaccine: the mother's age, her race/ethnicity, her self-reported history of HPV disease, her age of sexual initiation, the daughter's age, dating status and anticipated age of sexual initiation, the number of sexual topics discussed and the mother's comfort with sexual conversations, mother's sexual values, and the family environment.

#### Qualitative/hypothesis generating results

The mothers were asked if they were offered the vaccine. If their daughter had not gotten the vaccine, then they were asked their intention (or lack of intention) to get the vaccine. These short answers were analyzed by vaccination and intent status. The mothers who had been offered the vaccine and reported a lack of intention to get it in the next 12 months, most commonly reported that there was not enough information about the vaccine and for some, a lack of urgency, because they perceived their daughters as having more than a year before they would be exposed. These answers were in contrast to those who had not had a conversation with their healthcare provider and did not intend to get it in the next 12 months. Three of these mothers, in contrast to none of the other mothers, appeared to be against the vaccine (e.g., "We teach our children that love and sex

are for marriage only"). More of the mothers who had not been counseled about the vaccine gave vague answers about their daughters' lack of sexual activity. There were nine mothers who reported that their daughters should explore their sexuality as long as they take care of themselves, yet had not gotten the vaccine for their daughters when offered or did not intend to get the vaccine in the next 12 months. Five of those mothers, and an additional 10 mothers (15 total), reported that they thought their daughters would have sexual intercourse by the end of high school. These mothers either failed to fill out the qualitative portion, indicated a desire to have more information about the vaccine or that their daughter seemed young. (She is only 12, sex is far away.) One mother indicated that she intended to vaccinate her daughter but that, "My daughter was scared and crying that day at the doctor discussion."

#### Discussion

Prior to the approval of the HPV vaccine, there was concern that the sexual transmission of the pathogen would provide a barrier to universal adolescent uptake because of stigma associated with STIs and reluctance to discuss adolescent sexuality. A variety of studies of parents' anticipated attitudes did not support this notion [2]. However, there has been limited direct assessment of sexual values and attitudes, and these studies were conducted prior to availability of the vaccine. In this study we examined the attitudes of mothers as the vaccine was newly launched. Because data collection occurred at the very beginning of availability, some parents were responding based on intent and others had actually had an opportunity to make a decision about the vaccine.

Consistent with the literature prior to the availability of the vaccine, most mothers in this study were accepting of the HPV vaccine and planned to have their daughters vaccinated. Objections to vaccination were largely centered around the newness of the vaccine, and thus, not having enough information regarding safety and efficacy or the daughters being "too young" when they were in early adolescence was of some concern. Although the study was not designed to examine the process of and the impact of physician counseling, it appeared that those who had been counseled had more positive attitudes toward the vaccine and understood better the reasons for vaccinating their daughters prior to initiation of sexual activity. It is also interesting that the age of the daughter was not predictive of vaccination status; yet many parents who had not gotten the vaccine or did not intend to get the vaccine stated young age as a reason.

The importance of physician counseling is consistent with previous studies that demonstrated that following counseling, more parents are more in favor of vaccination [30,31]. However, the stated need for more information reported even by those who had presumably received coun-

seling about the vaccine may provide logistic challenges for the providers. New vaccines may require additional time for counseling, which in a busy clinic may present a barrier. Although there have been several recent additions to the recommendations for adolescents, this is the only vaccine for a disease that was not previously vaccine preventable. For example, parents were already familiar with vaccinating their babies for pertussis, and most have some awareness that college students and/or military recruits are vaccinated for meningococcal disease. Clearly, counseling is an important part of vaccine uptake, as others have shown that parents want to have their concerns heard and that trust in authority figures helps to manage the response to antivaccination messages [32,33]. Future studies should examine the form that vaccine counseling should take and its impact on vaccine uptake. For example, with regard to the HPV vaccine, one could investigate the impact on uptake of a strongly worded recommendation versus greater information either about the safety, efficacy, or sexual transmission of the vaccine.

In this study, we found that mothers with a high school degree or less were more likely to have their daughter immunized. This is consistent with others' findings regarding vaccine acceptability [33–35]. In addition, although young children in poverty are more likely to be undervaccinated or not "up to date" on their vaccines, unvaccinated children are more likely to come from families where the mother is college educated and the family has a high household income [36]. In the current study, all of the families were accessing health care; thus, the traditional barriers for disadvantaged families may have been less of an issue for them.

Consistent with Zimet's findings [8] regarding STI vaccines, the mothers with an STI history were more likely to have vaccinated their daughters. These mothers may have viewed their daughters as more vulnerable to STIs, and therefore felt a greater sense of urgency to vaccinate, a stance in marked contrast to the general lack of urgency expressed by some of the mothers who had not, or did not intend to, immunize their daughters against HPV.

Mothers who provided more direct monitoring when their daughters were with peers were found to be more likely to vaccinate. This finding is of interest in light of the fact that parental supervision has been found to be related to decreases in sexual risk taking [22,13–15]. Thus, it was those parents whose young adolescents may have been at less risk that were more likely to protect their daughters through immunization. This finding supports the notion that for most parents the decision to vaccinate one's daughter for HPV reflects parenting styles and vaccination attitudes rather than a probabilistic assessment of risk based on the route of transmission [2]. This indicates an approach to parenting that focuses on providing the most protection for their children across domains.

Finally, those mothers who had daughters who would not mind shots were more likely to vaccinate their daughters, which is similar to the finding of others that rejectors of vaccination report disliking needles and pain [34]. Others have found that a dislike of needles is related to vaccine rejection. This finding serves as a reminder to clinicians that the vaccine process and the subsequent tears associated with getting a shot can be stressful for parents and their adolescents. Thus, it may be important to address fear of shots as part of the counseling process. Accurate and supportive information will need to be provided to families.

There are several limitations to this study. It was conducted in a university-based primary care clinic, which has a large vaccine center. As part of the vaccine center's activities, there is an active vaccine clinical trials program housed in the primary care clinic, which conducted one of the adolescent HPV vaccine trials. In addition, the vaccine center houses the National Network for Immunization Information [37], which routinely provides education on vaccine safety, and the dangers of mis-information. Thus, the care providers and the families are exposed to accurate information about vaccines and may be more positive about vaccines than in other settings. The sample size was relatively small; therefore, it is possible that we did not have sufficient power to detect some real differences between groups. The design of the study did not allow for us to know which girls were currently sexually experienced and the degree to which the parents' intentions matched their actual behaviors in the next 12 months. Intention to vaccinate is typically a good, but rather imperfect predictor of subsequent behavior, with studies showing an average intention–behavior correlation of .47 [38].

Despite these limitations, this study provides critical information about mothers' attitudes during the first months of HPV vaccine availability. The findings support the results of research focused on attitudes towards hypothetical HPV/STI vaccines. Mothers' decisions about the HPV vaccine were related to their parenting, sense of vulnerability, and vaccine attitudes. Mothers who were not planning to vaccinate did not appear to not feel an urgency given the newness of the vaccine, and many planned to vaccinate eventually.

## Acknowledgments

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# **EXHIBIT 282**



DICTIONARY

THESAURUS

# anti-vaxxer noun



Save

Word

an-ti-vax-xer | \,an-tē-'vak-sər , an-tī-\*plural* **anti-vaxxers**

## Definition of *anti-vaxxer*

: a person who opposes [vaccination](#) or laws that mandate vaccination

// As *anti-vaxxers* launch a campaign against a bill that would eliminate their ability to opt out of required shots, supporters of the proposal are delivering more than 21,000 petition signatures to the office of state Sen. Ben Allen ...

— Alexei Koseff

## First Known Use of *anti-vaxxer*

2009, in the meaning defined [above](#)

## Learn More about *anti-vaxxer*

### Share *anti-vaxxer*



### Time Traveler for *anti-vaxxer*



The first known use of *anti-vaxxer* was in 2009

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[anti-vaccine](#)

[anti-vax](#)

**[anti-vaxxer](#)**

[anti-vehicle](#)

[antivenin](#)

### Statistics for *anti-vaxxer*

**Look-up Popularity**

Bottom 10% of words

# **EXHIBIT 283**

## informed consent

*n.*

Consent by a person to undergo a medical procedure, participate in a [clinical](#) trial, or be counseled by a professional such as a social worker or lawyer, after receiving all material information regarding risks, benefits, and alternatives.

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# **EXHIBIT 284**



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## ETHICS

## Informed Consent



## Code of Medical Ethics Opinion 2.1.1

Informed consent to medical treatment is fundamental in both ethics and law. Patients have the right to receive information and ask questions about recommended treatments so that they can make well-considered decisions about care. Successful communication in the patient-physician relationship fosters trust and supports shared decision making.

### CME course: Informed consent and decision making

This e-learning module will help physicians identify the standard process of informed consent and how to handle situations when patients cannot give informed consent.

[Go to Course](#)

The process of informed consent occurs when communication between a patient and physician results in the patient's authorization or agreement to undergo a specific medical intervention. In seeking a patient's informed consent (or the consent of the patient's surrogate if the patient lacks decision-making capacity or declines to participate in making decisions), physicians should:

(a) Assess the patient's ability to understand relevant medical information and the implications of treatment alternatives and to make an independent, voluntary decision.

(b) Present relevant information accurately and sensitively, in keeping with the patient's preferences for receiving medical information. The physician should include information about:

1. The diagnosis (when known)
2. The nature and purpose of recommended interventions

3. The burdens, risks, and expected benefits of all options, including forgoing treatment

(c) Document the informed consent conversation and the patient's (or surrogate's) decision in the medical record in some manner. When the patient/surrogate has provided specific written consent, the consent form should be included in the record.

In emergencies, when a decision must be made urgently, the patient is not able to participate in decision making, and the patient's surrogate is not available, physicians may initiate treatment without prior informed consent. In such situations, the physician should inform the patient/surrogate at the earliest opportunity and obtain consent for ongoing treatment in keeping with these guidelines.

AMA Principles of Medical Ethics: I, II, V, VIII

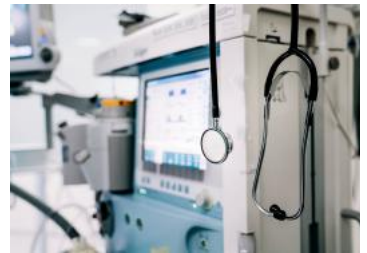
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**When life support is withdrawn, commitment to care must not end**

**Caring for patients at the end of life**

# **EXHIBIT 285**

> [Obstet Gynecol.](#) 2004 Dec;104(6):1465-6. doi: 10.1097/00006250-200412000-00048.

## ACOG Committee Opinion No. 306. Informed Refusal

ACOG Committee on Professional Liability

PMID: 15572515 DOI: [10.1097/00006250-200412000-00048](#)

### Abstract

Informed refusal is a fundamental component of the informed consent process. Informed consent laws have evolved to the "materiality or patient viewpoint" standard. A physician must disclose to the patient the risks, benefits, and alternatives that a reasonable person in the patient's position would want to know to make an informed decision. Throughout this process, the patient's autonomy, level of health literacy, and cultural background should be respected. The subsequent election by the patient to forgo an intervention that has been recommended by the physician constitutes informed refusal. Documentation of the informed refusal process is essential. It should include a notation that the need for the intervention, as well as risks, benefits, and alternatives to the intervention, and possible consequences of refusal, have been explained. The patient's reason for refusal also should be documented.

### LinkOut – more resources

Full Text Sources

[Ovid Technologies, Inc.](#)

# **EXHIBIT 286**



The American College of  
Obstetricians and Gynecologists  
WOMEN'S HEALTH CARE PHYSICIANS

# COMMITTEE OPINION

Number 564 • May 2013

(Reaffirmed 2016)

## Committee on Ethics

*This Committee Opinion was developed by the Committee on Ethics of the American College of Obstetricians and Gynecologists as a service to its members and other practicing clinicians. Although this document reflects the current viewpoint of the College, it is not intended to dictate an exclusive course of action in all cases. This Committee Opinion was approved by the Committee on Ethics and the Executive Board of the American College of Obstetricians and Gynecologists.*

## Ethical Issues With Vaccination for the Obstetrician–Gynecologist

**ABSTRACT:** Because of the growing importance of infectious disease prevention in the individual patient and the larger community, it is vital that Fellows of the American College of Obstetricians and Gynecologists be prepared to navigate the practical and ethical challenges that come with vaccination. Health care professionals have an ethical obligation to keep their patients' best interests in mind by following evidence-based guidelines to encourage patients to be vaccinated and to be vaccinated themselves. College Fellows should counsel their patients about vaccination in an evidence-based manner that allows patients to make an informed decision about the use of these agents in their health care. The Centers for Disease Control and Prevention reports that no evidence exists of risk to the fetus from vaccinating pregnant women with noninfectious virus or bacterial vaccines or toxoids. Mandatory vaccination of health care professionals may be an ethically justified strategy in cases in which the harm to patients and the general population is believed to outweigh the autonomy of individual physicians.

Fellows of the American College of Obstetricians and Gynecologists (the College) have assumed an important role in the successful vaccination of women, both in the course of well-woman and prenatal care. Because vaccine-preventable infectious diseases cause morbidity and mortality that sometimes affects the fetus as well as the pregnant woman, the timely and effective vaccination of women has become a clinical priority for College Fellows. Given the scope of obstetrics and gynecology, these efforts help address the health of women across the full spectrum of their lives.

In their role as providers of well-woman care, obstetrician–gynecologists are in a position to advocate vaccination of the general adolescent and adult female patient population against infectious disease as part of routine care. Vaccinations are appropriately part of routine periodic assessments, underscoring the continuing role obstetrician–gynecologists play in the maintenance of women's health (1). Tetanus vaccinations serve as a leading example of the routine vaccines that women of reproductive age receive in the course of well-woman care.

The preconception and postpartum periods are other prime opportunities for vaccination against potentially dangerous or teratogenic infectious agents, such as rubella, that could affect future pregnancies (2). Vaccinations also play a central role in the prevention and control of acute outbreaks, as in the case of seasonal influenza or pandemics.

Recent attention has focused on potentially preventable human papillomavirus (HPV) infections among adolescent girls, and safety concerns about the vaccination of pregnant women during pandemic events have highlighted a number of ethical issues inherent in the allocation and administration of vaccinations among the patient population receiving care from obstetrician–gynecologists (3). At the same time, issues also have arisen about the role of physicians (obstetricians and gynecologists) in the mitigation of pandemics through compliance with stringent vaccination guidelines and allocation schemes for patients and health care workers. Given the growing importance of vaccination in clinical practice, it is vital that College Fellows be familiar with the

leading issues that attend the use of vaccines. Therefore, the Committee on Ethics makes the following recommendations:

- It is important for College Fellows to recognize that they have responsibilities to both the individual patient and the general population.
- It is a physician's responsibility to be knowledgeable about current standards of practice regarding vaccines, including their indications, benefits, and risks.
- College Fellows should counsel their patients about vaccination in an evidence-based manner that allows patients to make an informed decision about the use of these agents in their health care. Withholding vaccination or information about vaccinations is unacceptable because it violates the ethical obligations to respect patient autonomy and promote patient safety.
- Health care professionals are obligated to serve their patients' best interests by following authoritative guidance on vaccination for patients and clinicians, where medically appropriate and based on the best available evidence.
- The vaccination of adolescents poses unique ethical challenges for obstetrician-gynecologists related to privacy, confidentiality, and informed consent. College Fellows should respect the importance of protecting adolescents' access to reproductive health care services, including HPV vaccination, while adhering to local and national professional norms and applicable legal requirements.
- Current available evidence regarding the safety and efficacy of vaccinations should be reviewed and recognized. College Fellows should counsel their pregnant patients about vaccination in an evidence-based manner that allows patients to make an informed decision about their use. The Centers for Disease Control and Prevention (CDC) reports that no evidence exists of risk to the fetus from vaccinating pregnant women with noninfectious virus or bacterial vaccines or toxoids.
- To avoid their own personal contribution to the spread of disease, College Fellows have an ethical obligation to follow recommendations for vaccination themselves and other safety policies put into place by their local or national public health authorities such as the CDC and the College. Any perceived burdens or potential risks to clinicians themselves from vaccination do not supersede their responsibility to limit the spread of potentially harmful infectious disease.

### **Ethical Principles of Vaccination**

The goals of vaccination are to preserve the health of individual patients as well as the health of the general

public. When the health of the individual is considered, vaccines are administered to protect the health of a single patient or, in the case of a pregnant woman, the patient and her fetus. The benefit of preventing disease in the individual also promotes public health because once immune, she will not serve as a source of contagion for others. The achievement of population immunity through the vaccination of the community slows and may prevent the spread of a communicable disease through the larger population, thereby reducing the risk to individuals from that infectious agent.

Because of these separate but related purposes, vaccinations bring to light the relationship between the ethics of individual care and the ethics of public health. It is important for College Fellows to recognize that they have responsibilities to both the individual patient and the general population. In the vast majority of cases, the goals of promoting individual and public health are aligned.

The traditional clinical ethics with which most health care professionals are familiar focuses on the health and the well-being of the individual patient (4–8). Under this model, respect for autonomy and promotion of the well-being of the individual patient are the focus of medical efforts and, in many cases, might be given precedence over the perceived interests of the population at large (4, 9). In a public health-centered ethical framework, the health of the community would be given priority over that of the individual. The public health framework reflects the ethical theory of utilitarianism, which requires actions that result in the greatest good for the greatest number (10). The need to strike a balance between these two “goods” (ie, a healthy individual who is able exercise her autonomy and a healthy community) is familiar to women's health physicians. They face this issue when considering how to allocate often-limited health care resources to patients or how to reduce risks to sexual partners of patients with sexually transmitted infections to prevent further spread.

In providing vaccines to patients, clinicians must weigh these different sets of interests. Matters can become even more complicated for health care professionals, who must consider their own interests, rights, and responsibilities when presented with the professional expectation of being vaccinated themselves in order to protect patients regardless of whether they personally have objections to or concerns about vaccination. This tension can generate ethical challenges for College Fellows.

### **Ethical Issues in Allocation of Vaccines**

#### **Distribution of Limited Resources**

In rare circumstances, vaccine availability can be limited because of increased demand or decreased supply or both. In cases of limited availability, allocation strategies may be developed by health care or regulatory authorities to prioritize vaccine administration to specific subsets of the



population, such as children, pregnant women, or the medically vulnerable. In these circumstances, health care professionals play an important role in communicating the nature and purpose of such protocols to all patients, while simultaneously trying to fulfill their duty to address the health needs of the population as a whole.

Allocation strategies that limit access for certain groups to enhance access for other groups can generate conflict for patients and clinicians. Strategies to allocate limited resources typically involve some agreed upon basis for prioritization. At their foundation, these strategies are intended to protect more medically vulnerable members of the population, such as the elderly, pregnant women and their fetuses, and children, while also creating structures to maximize overall benefit for the community (such as the vaccination of health care workers and other key workers to minimize risk of dissemination and to protect the public infrastructure). Consistent with this approach, priorities are established that reduce the morbidity and mortality resulting from the spread of the infectious agent through the general population. In doing so, these plans should be designed not to exaggerate disparities among diverse populations that may already face barriers to health care. A recent Committee Opinion addresses ethical concerns of vaccine allocation in the context of a pandemic and examines strategies that include the priority typically given to pregnant women (3).

It is critical that health care professionals understand and comply with guidelines and recommendations regarding vaccination administration and allocation promulgated by local or regional health care jurisdictions. This will be particularly important when they encounter patients who are unfamiliar with the principles underlying the recommendation or who perceive the allocation strategies as unjust or discriminatory. College Fellows should be prepared to explain to patients the importance of and the rationale for allocation mechanisms while continuing to address their patients' health care needs through alternative strategies other than vaccination. College Fellows also should be willing to provide professional expert advice to local public health jurisdictions in determining allocation and distribution guidelines.

### **Health Care Professionals Are Instrumental to Successful Vaccination Strategies**

College Fellows can play a key role in successful vaccination strategies both through education and administration of vaccines as indicated. They are obligated to serve their patients' best interests by following authoritative guidance on vaccination for patients and clinicians, where medically appropriate and based on the best available evidence. Despite the recognized importance of vaccinations in preventing illness, barriers remain to the timely and effective vaccination of patients and health care professionals.

One barrier arises as some health care professionals continue to express concern about the safety of vaccines, particularly their use in pregnant women, and allow these concerns to alter their advice to patients. Current available evidence regarding the safety and efficacy of vaccinations should be reviewed and recognized. College Fellows should counsel their pregnant patients about vaccination in an evidence-based manner that allows patients to make an informed decision about the use of these agents in their health care. The CDC reports that no evidence exists of risk to the fetus from vaccinating pregnant women with noninfectious virus or bacterial vaccines or toxoids (11). However, a recent survey demonstrated that the concerns of a subset of obstetrician–gynecologists about vaccine safety and potential liability interfere with compliance with recommendations from the College and the CDC (12). This phenomenon was witnessed during the 2009 H1N1 influenza pandemic, during which some clinicians withheld vaccinations during the first trimester of pregnancy (despite clinical practice guidelines to the contrary) out of concerns for increased risk of teratogenic effects on the fetus (13, 14). This type of practice pattern is ethically problematic because it is counter to evidence-based patient care, a goal that is always important but particularly so among a population that is medically vulnerable during an infectious pandemic. Withholding vaccination or information about vaccinations is unacceptable because it violates the ethical obligations to respect patient autonomy and promote patient safety.

Financial and business concerns may present another barrier to vaccination practices. In a survey of obstetrician–gynecologists, almost one half found the cost and infrastructure needed to stock and administer specific vaccines to be a major challenge; insurance reimbursements were insufficient to outweigh the financial and practical challenges to offering vaccination (15). In another study, obstetrician–gynecologists expressed limited availability of time and resources to provide vaccines as a routine part of care (12). If financial or business concerns limit a physician's ability to provide vaccinations in his or her practice, the physician should provide information about alternative sources for vaccination and, when possible, refer patients to alternative community sources such as state or local health department clinics.

It is important that College Fellows educate themselves about relevant infectious agents and all possible mitigation strategies. It is a physician's ethical responsibility to be knowledgeable about current standards of practice regarding vaccines, including their indications, benefits, and risks. Their clinical practice should incorporate up-to-date evidence-based practices. Health care professionals should actively participate in efforts to develop strategies to address infectious disease control through education and patient access to vaccinations. In these ways, health care professionals can serve the best interests of their patients within the constraints of their practice environment.

## Informed Consent and Patients' Decision Making Regarding the Use of Vaccinations

Informed consent is a core component of the ethical clinical relationship (10). As with all forms of medical therapy, informed consent must precede vaccination administration. In the informed consent discussion, health care professionals must discuss information central to the decision-making process for vaccination, including the indications, risks, and benefits of the vaccine and available alternatives, as well as possible consequences from nonvaccination (16). Data to inform these discussions are available to both health care professionals and the general public through Vaccine Information Statements found on the CDC's web site (<http://www.cdc.gov/vaccines/pubs/vis>). Federal law requires that a Vaccine Information Statement be given to patients (or their parents or guardians) before each dose of certain vaccines.

Because some vaccines are developed in the midst of an emergent infectious event, patients may raise questions about long-term consequences of an urgently developed vaccine. These questions should be integrated into the decision-making process, with the clinician listening to the patient's concerns and recognizing that information evolves over time while also making every reasonable effort to address fears that are not justified by scientific data. In these discussions, clinicians should emphasize the safety and benefit profiles of vaccines as outlined generally in the literature and by their respective professional organizations and national authorities such as the CDC. They should also include a discussion of the distinct benefits and risks as well as uncertainties of the vaccine's use in pregnant women, and the benefits and risks of nonvaccination. As mentioned in the previous section, the CDC reports that no evidence exists of risk to the fetus from vaccinating pregnant women with noninfectious virus or bacterial vaccines or toxoids (11). Recent reports indicate that influenza immunization of pregnant women is highly effective in reducing hospitalization related to influenza-like illness of their infants for up to 6 months of age (17, 18).

In addition, health care professionals should respect patients' informed refusal of vaccinations. For some patients, receiving vaccines conflicts with personal or cultural beliefs (19). For others, the perceived uncertainty of scientific research on vaccine safety hinders their acceptance of clinical recommendations for vaccination, despite the safety profile of vaccines and demonstrated benefit to pregnant patients (13). This issue commonly arises in the context of pregnancy, where research on pregnant women has been more limited than research involving other segments of the population (20). In such cases, health care professionals should counsel patients thoroughly about the risks of nonvaccination for themselves, household members who could be affected, and

the population at large. In cases where vaccination is declined, although termination of the physician-patient relationship is a possible option, it is often counterproductive and disruptive. Instead, College Fellows have the opportunity to put alternative strategies into place to protect the health of the patient and that of the general community. Such strategies include patient education to monitor and manage symptoms at home and behavioral approaches to reduce risk associated with infection and transmission. Although these strategies help to mitigate harms, they continue to be inferior in reducing risk compared to vaccination, and patients who refuse vaccination should be aware of the potential consequences of depending on alternative approaches to infection control.

Another component of patients' decisions regarding infection control and prevention is the possibility of participation in clinical trials for newly developed vaccines. Clinical vaccine research is an important step in the translation of knowledge from the laboratory to patient care. Participation in clinical trials is a choice generally available to many patients as they consider all their health care options, including interventions as part of standard care or clinical research. Although exceptions do exist, pregnant women are typically excluded from initial and some postmarketing stages of drug trials principally out of concern for the possible effects of the drug on the fetus. The ethical and practical consequence of this exclusion is a limitation of information about vaccine safety and efficacy for pregnant women and the fetus (20). The lack of long-term data, in turn, has a direct influence on the quality of care delivered to pregnant women and the ability of patients to make informed decisions about vaccination during pregnancy. Only by developing well-designed trials that safely include pregnant women will the necessary outcomes and safety data become available. Efforts should be made to open research trials to pregnant women, when possible.

Adolescents also seek reproductive and sexual health care, and this brings challenges that must be addressed (21). The vaccination of adolescents poses unique ethical challenges for obstetrician-gynecologists relative to privacy, confidentiality, and informed consent. Because gynecologic practice often includes care for adolescents, College Fellows face a particular set of ethical challenges associated with vaccination intended to promote their sexual health. The recent availability of vaccination for HPV exemplifies the ethical issues associated with providing care to minors; HPV vaccination guidelines recommend that girls and women aged 9–26 years of age be immunized (22, 23). College Fellows should respect the importance of protecting adolescents' access to reproductive health care services, including HPV vaccination, while adhering to local and national professional norms and applicable legal requirements for parental consent or notification.

Traditionally, minors may provide informed assent rather than consent for medical therapies. In contrast

to informed consent, informed assent entails involving young patients in discussions and decisions about their care as appropriate for their developmental stage. This approach respects the developing independence and autonomy of minors by allowing them to be involved in their medical decision making, while acknowledging the need to obtain authorization to treat from their parents or guardians (24). Informed assent from the minor patient before treatment should always be the goal of the health care provider. The adolescent deserves a careful age-appropriate discussion of the benefits and potential risks of any treatment, including vaccination. Careful assessment of the need for treatment and the functional role of the parent in guidance and support for the minor patient facing a health care decision are also required.

With some exceptions, this practice holds true for adolescents seeking vaccinations. In all states, statutes addressing the treatment of minors allow adolescents younger than 18 years access to testing and treatment for sexually transmitted infections (25). Policies regarding adolescents' ability to independently access the HPV vaccine are currently under debate (26, 27). The College remains a strong advocate for respecting adolescents' confidentiality as a way to minimize any barriers in their sexual and reproductive health care (21). It is important that College Fellows familiarize themselves with the laws, regulations, and policies in their jurisdictions, particularly as these guidelines evolve with public and professional discussions.

### **Vaccination of Health Care Professionals**

College Fellows should recognize the personal role that they play in preventing transmission of infectious agents. Because clinicians come into contact with numerous potentially vulnerable patients throughout the day, they may become infected and be sources for transmission of highly contagious diseases. To avoid their own personal contribution to the spread of disease, College Fellows have an ethical obligation to follow recommendations for vaccination themselves and other safety policies put into place by their local or national public health authorities such as the CDC and the College. Any perceived burdens or potential risks to clinicians themselves from vaccination do not supersede their responsibility to limit the spread of potentially harmful infectious disease.

Several perspectives support this ethical imperative that health care professionals be vaccinated when clinically appropriate. First, data demonstrate that vaccination among health care professionals can reduce the spread of infectious disease throughout inpatient and outpatient populations (28). Second, vaccination prevents infectious illness among medical staff, thus minimizing the use of health care resources that could be used for patients and the general population. Third, with the prevention of illness, fewer physicians will be absent because of illness, potentially increasing the number of health care person-

nel available during times of an infectious outbreak (28). Finally, in being compliant with medically appropriate vaccination strategies, health care professionals send an important message to their patients about the benefits of vaccination, which may, in turn, increase their patients' willingness to be vaccinated.

Despite the evidence pointing to the benefit of vaccination, compliance with voluntary vaccination programs for health care professionals has been disappointing. Some of the leading reasons cited for noncompliance were perception of low risk of contracting the infectious agent, diminished perception of the potential severity of an infectious outbreak, fear of adverse events from vaccination, and lack of time and opportunity for vaccination (29, 30). Thus, consideration of mandatory vaccination has emerged in response to poor compliance rates among physicians. Mandatory vaccination of health care professionals may be an ethically justified strategy in cases in which the harm to patients and the general population is believed to outweigh the autonomy of individual physicians (31–35). Mandates should be put in place only if supported by valid data about the efficacy and safety of the vaccine. In addition, public health plans that include mandatory vaccination will be most beneficial if they are developed in cooperation with key stakeholders and consider the needs of individual practitioners, institutions, and communities.

Any such vaccine mandates should include recognized exceptions for medical contraindications as well as an active opt-out mechanism for those physicians who profess conscientious objections to vaccination; however, practitioners should be reminded that there is a high standard applied to the qualification of conscientious objections of those who decline. Trivial justifications may not be recognized.

Those who elect to opt out of vaccination also must recognize the potential harm they are bringing to patients and their local health care environment because of their choice to refuse vaccination. In the case of a live vaccine where the recipient may serve as a possible source of transmission of the agent to pregnant patients or patients with compromised immune systems, the risk of harm to patients might outweigh the benefit based on the patient population being served. In such cases, other strategies should be in place to protect the health of patients should clinicians themselves become ill. Preemptive plans, such as the mandatory use of respiratory masks and other mechanisms including contact precautions to facilitate infection control, will be vital for these individuals and should be developed in conjunction with local infectious disease experts and institutional administrators.

Although clinician vaccination is the best protective strategy for his or her patients, voluntary absenteeism by the clinician in the case of illness is another strategy, albeit less than sufficient to protect patient health. Such a strategy is flawed because it does not protect the patient in the period of asymptomatic infec-

tion. Furthermore, clinicians must also clearly recognize that absenteeism is not an effective alternative to vaccination because it ultimately compromises the care of patients and populations in the setting of a pandemic by removing their services from the environment.

Physicians should recognize that there also may be potential professional consequences for themselves from declining vaccination. For example, loss of employment may result if their employer makes vaccination a condition of employment.

## Conclusion

Vaccines continue to play an essential role in the care delivered by College Fellows. Because of their growing importance in the prevention of infectious disease in the individual patient and the larger community, it is vital that College Fellows be prepared to navigate the practical and ethical challenges that come with vaccination. Included in these considerations is the decision for College Fellows to become vaccinated and, if the decision is made to opt out of vaccination, to be cognizant of the potential consequences to themselves and their patients. Health care professionals have an ethical obligation to keep their patients' best interests in mind by following evidence-based guidelines to encourage patients to be vaccinated and to be vaccinated themselves.

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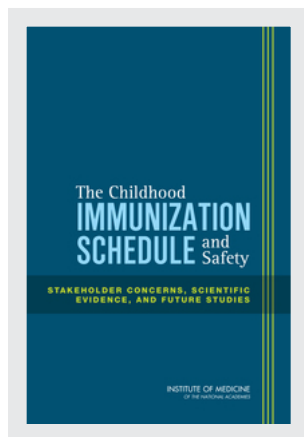
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## The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies (2013)

### DETAILS

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## Summary

### BACKGROUND

Vaccines are among the most effective and safe public health interventions available to prevent serious disease and death. As the incidence of vaccine-preventable diseases has declined because of the widespread use of immunizations, potential adverse effects of the vaccines themselves have taken on greater saliency among stakeholders. The U.S. Advisory Committee on Immunization Practices (ACIP) has created a schedule of vaccines that should be administered at various intervals. ACIP recommends immunization with vaccines that protect young children (age 6 years and under) against 14 pathogens (see Appendix A) and strives to protect children at the youngest age necessary to shield them from diseases when they are the most vulnerable. The childhood immunization schedule (defined in this report as the immunization schedule covering children from birth through age 6 years) immunizes children in a manner consistent with demonstrated efficacy, safety, and feasibility but also permits some degree of flexibility to accommodate individual preferences and logistics.

With the current schedule, children may receive up to 24 immunizations by age 2 years and up to 5 injections in a single visit. Although the number of vaccines has increased over the years to protect against a greater number of diseases, because of technological advances children now receive fewer antigens, which are the components of vaccines that stimulate the immune system.

In the United States, manufacturers extensively test new vaccine products and then the federal government undertakes a formal process of review

and approval before vaccines are made publicly available. Each new vaccine considered for inclusion in the immunization schedule is tested within the context of the existing schedule and reviewed by clinical researchers, who analyze the balance of demonstrated benefits and risks. Thus, each new vaccine is approved on the basis of a detailed evaluation of both the vaccine itself and the immunization schedule. Every year, the Centers for Disease Control and Prevention (CDC) issues guidance on the vaccines to be administered and immunization schedules for children, adolescents, and adults, based on recommendations from ACIP.

To recommend new vaccines, ACIP uses a process in which it reviews a comprehensive set of data associated with the vaccine, including illnesses and deaths associated with the disease and specific high-risk groups; the results of clinical trials, including indicators of safety, efficacy, and effectiveness; cost-effectiveness; information on vaccine use provided by the manufacturer in the product's labeling or package insert; and the feasibility of incorporation of the vaccine into the existing immunization schedule.

Ongoing surveillance systems are the primary source of data on vaccine safety postmarketing. CDC maintains three major postmarketing surveillance systems: the Vaccine Adverse Event Reporting System, which is jointly managed with the Food and Drug Administration (FDA); the Vaccine Safety Datalink (VSD); and the Clinical Immunization Safety Assessment Network. In addition to the surveillance systems managed by CDC, FDA has established the Sentinel Initiative, a supplementary mechanism for monitoring vaccine safety.

Immunization coverage among children entering kindergarten currently exceeds 90 percent for most recommended vaccines. However, concerns about vaccine safety have contributed to increases in the delay or refusal of immunization, which have, in turn, contributed to a reemergence of vaccine-preventable illnesses. For example, measles and pertussis (whooping cough) outbreaks have occurred in areas where higher proportions of children are unimmunized.

Vaccines—like all drugs or medical interventions—are neither 100 percent risk-free nor 100 percent effective. Additionally, population-wide prevention of vaccine-preventable diseases relies on community immunity, also commonly referred to as herd immunity, which is the shared protective effect conferred on unimmunized individuals when a sufficiently large proportion of the population is immunized against infectious diseases. This phenomenon is achieved when too few people who are vulnerable to development of a disease remain in the population to maintain the chain of disease transmission. Community immunity is waning, however, in places with increasing numbers of unimmunized, incompletely immunized individuals and/or individuals with waning immunity.

Even though children are required to be immunized to enter school

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and child care, medical exemptions are allowed in all states, and almost all states allow immunization exemptions for people who have religious beliefs against them. Furthermore, 20 states permit exemptions for those who object to immunizations because of personal, moral, or other beliefs.

## THE COMMITTEE

The National Vaccine Program Office (NVPO) of the U.S. Department of Health and Human Services (HHS) asked the Institute of Medicine (IOM) to convene a committee of experts in pediatrics, neurology, medical ethics, immunology, statistics, epidemiology, and public health to identify feasible study designs to explore the safety of the U.S. childhood immunization schedule. A 14-member committee was assembled to address the statement of task. The committee's charge is independent of the charges for previous IOM vaccine studies, and committee members were selected to avoid any real or perceived biases or conflicts. Strict criteria for membership prevented members from having financial ties to vaccine manufacturers or their parent companies, previous service on federal vaccine advisory committees, or having delivered expert testimony or written publications on vaccine safety. The committee's charge is detailed in Box S-1.

## COMMITTEE PROCESS

To complete its charge, the committee held three information-gathering meetings in two locations. Before the first meeting and throughout the committee's deliberations, the committee gathered information on public

**BOX S-1**  
**Statement of Task**

The Institute of Medicine will convene an expert committee to

1. Review scientific findings and stakeholder concerns related to the safety of the recommended childhood immunization schedule.
2. Identify potential research approaches, methodologies, and study designs that could inform this question, including an assessment of the potential strengths and limitations of each approach, methodology and design, as well as the financial and ethical feasibility of doing them.
3. Issue a report summarizing their findings.

perspectives and reviewed the scientific literature on the safety of the recommended childhood immunization schedule. At the public forums, the committee heard presentations by pediatricians, representatives of federal and state agencies and public health agencies in other countries, vaccine safety researchers, advocacy groups, vaccine manufacturers, and methodological experts. The committee invited comments (both written and oral) from the general public and representatives from numerous organizations with an interest in vaccine safety.

The committee held five deliberative meetings over 6 months. To address its charge, the committee requested from consultant Martin Kulldorff a commissioned paper on study designs that could be used to assess the safety of the immunization schedule (see Appendix D). The paper was intended to provide methodological input to the committee but the paper does not necessarily reflect the committee's views. To solicit stakeholders' feedback, the commissioned paper was posted on the committee's website.

## STAKEHOLDER CONCERNS

A review of the scientific literature, as well as a detailed review of the oral and written public comments, revealed that among the various stakeholder groups,<sup>1</sup> parents, health care providers, and public health officials share the sentiment that there is insufficient communication between providers and parents about the schedule's safety. Even though the vast majority of parents adhere to the ACIP-recommended immunization schedule, some parents are concerned that the schedule may present unnecessary risks because of the timing and number of vaccinations.

Some parents request variations in the immunization schedule, such as a delay of one or more immunizations or the administration of fewer vaccinations at each visit. Some parents also refuse immunizations entirely on the basis of the premise that their children's risks from vaccine-preventable diseases are less than the risks of adverse events associated with immunizations. Such decisions may reflect, in part, the significant and sustained decline in vaccine-preventable diseases that immunization policy has achieved in the past several decades and against which the risk of even extremely rare adverse events may be seen as not worth taking. Some parents are concerned about their child's risk of complications after immunization on the basis of a family history or the child's medical condition and thereby

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<sup>1</sup>Stakeholder groups include researchers; advocacy groups; federal agencies and advisory committees; the general public (including parents); the health care system and providers; international organizations; media; nongovernmental organizations; philanthropic organizations; state, local, and tribal government agencies; industries, such as travel and vaccine manufacturing industries; vaccine distributors; and investors in vaccine manufacturers.

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decide to delay or omit immunizations. Other parents express a general lack of confidence in U.S. government decisions about the safety and benefits of the childhood immunization schedule.

The committee understands that these parental concerns are an expression of concern and a way to care for their children's health and well-being. However, the committee also recognizes that a delay or refusal to immunize their children has already contributed to outbreaks of disease across the United States that pose a risk to the health of many people, particularly those with compromised immune systems.

The committee's review of the literature also focused on factors that affect public trust in vaccination campaigns and information on vaccines. Improved communication between public health authorities and parents will require improvements to the clarity of information as well as the building of trust and the use of a systematic approach to elicit public concerns. Further research into questions that parents seek to answer by use of the scientific methods of social, behavioral, and decision science is indicated.

## HEALTH OUTCOMES

The committee searched for, assembled, and summarized evidence on the association between the immunization schedule and specific health conditions that was already published in the peer-reviewed literature. The health outcomes that the committee chose to review were selected on the basis of an examination of the peer-reviewed literature, previous IOM vaccine safety studies, and public presentations at open meetings of this committee. The number of studies that addressed aspects of the immunization schedule varied; for some outcomes, several studies had examined the cumulative effects of vaccines and adjuvants or preservatives, whereas very few studies could be found for other outcomes.

The committee's literature searches and review were intended to identify health outcomes associated with some aspect of the childhood immunization schedule. Allergy and asthma, autoimmunity, autism, other neurodevelopmental disorders (e.g., learning disabilities, tics, behavioral disorders, and intellectual disabilities), seizures, and epilepsy were included as search terms. Furthermore, the committee reviewed papers on immunization and premature infants.

In summary, few studies have comprehensively assessed the association between the entire immunization schedule or variations in the overall schedule and categories of health outcomes, and no study has directly examined health outcomes and stakeholder concerns in precisely the way that the committee was charged to address in its statement of task. No studies have compared the differences in health outcomes that some stakeholders questioned between entirely unimmunized populations of children and fully

immunized children. Experts who addressed the committee pointed not to a body of evidence that had been overlooked but rather to the fact that existing research has not been designed to test the entire immunization schedule.

The committee believes that although the available evidence is reassuring, studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted. Nevertheless, in its literature review, the committee found useful designs for studies to measure exposures and outcomes and identified strategies for expanding or adapting conventional study designs to clearly address whether any adverse health outcomes are associated with the overall immunization schedule.

## METHODOLOGICAL APPROACHES

Moving from an analysis of stakeholder concerns and the limited scientific evidence about the association between the immunization schedule and adverse events to recommendation of specific research methods and study designs to address that association is an ambitious task in light of the complexity and changing nature of the recommended immunization schedule. Variables such as the number of doses, the age of administration, and the amount of time between doses permit the examination of a large number of potential research questions. Among the many questions about the current immunization schedule that could be posed, the committee parsed the phrase “this question” in Part 2 of the statement of task (Box S-1) into four broad research questions of interest to stakeholders. These are identified in Box S-2.

The committee broadly considered several general research strategies that might be used to address these questions: randomized controlled trials (RCTs), prospective and retrospective observational studies, animal models, and secondary analyses of existing data.

### Randomized Controlled Trials

When it is possible to randomize study participants, the RCT is widely acknowledged to be the preferred study design for determining cause and effect. RCTs are currently used as part of the FDA approval process to evaluate the safety and effectiveness of individual vaccines in the context of the recommended immunization schedule. Although this is the strongest type of study design, the committee concluded that costs, the large number of participants that would be required, ethical concerns, and other factors make it an inappropriate design for addressing the research questions at hand.

RCTs require participants to be randomly assigned to a study group.



**BOX S-2****Leading Research Questions of Interest to Select Stakeholders**

1. How do child health outcomes compare between those who receive no vaccinations and those who receive the full currently recommended immunization schedule?
2. How do child health outcomes compare between (a) those who receive the full currently recommended immunization schedule and (b) those who omit specific vaccines?
3. For children who receive the currently recommended immunization schedule, do short- or long-term health outcomes differ for those who receive fewer immunizations per visit (e.g., when immunizations are spread out over multiple occasions), or for those who receive their immunizations at later ages but still within the recommended ranges?
4. Do potentially susceptible subpopulations—for example, children from families with a history of allergies or autoimmune diseases—who may experience adverse health consequences in association with immunization with the currently recommended immunization schedule exist?

However, the random placement of children into a study group in which they would receive less than the full immunization schedule or no vaccines would not be ethical because they would be exposed to a greater risk for the development of diseases and community immunity would be compromised. Furthermore, parents who reject vaccination likely would not allow their children to be randomized to the group that receives full immunization. Additionally, health care professionals serving participants placed in the group to receive fewer or no vaccines would have to go against professional medical guidelines that call on them to encourage patients to follow the recommended schedule.

Even the use of a dispersed immunization schedule that is still within the accepted ACIP time frame for vaccinations as a trial arm would require an increased number of clinic visits, often in rapid succession over a period of a few weeks, which could prove difficult and costly for both the clinics and participating families and may be unacceptable to insurers if its improved effectiveness—measured as a decreased rate of adverse outcomes—was negligible. Although the use of a different schedule that still conforms to the ACIP vaccination time frame is unobjectionable ethically, the committee cannot endorse this method as a feasible option.



The conduct of an RCT would require thousands of participants to be of sufficient size to answer questions about the outcomes of different immunization schedules, and the study would have to span at least 6 to 10 years, meaning that it would likely cost the nation tens of millions of dollars. The risks to participants' health, the cost and time involved, and the ethical challenges all make the conduct of an RCT unsuitable for addressing the research questions, at least until further work with secondary data has been conducted.

### New Prospective Observational Studies

Observational studies are another form of clinical research that can provide useful insights and information that may be used to answer research questions. The committee reviewed opportunities to study groups that choose not to vaccinate using a prospective cohort study design. However, such a study would not conclusively reveal differences in health outcomes between unimmunized and fully immunized children for two main reasons. First, to be informative, cohort studies require sufficiently large numbers of participants in each study group and the sample populations often suggested for use in a comparison of vaccinated and unvaccinated children (such as some religious groups) are too small to adequately power a comparative analysis, particularly in the case of rare adverse health outcomes. Because meaningful comparisons require thousands of participants in each study group and less than 1 percent of the U.S. population refuses all immunizations, the detection of enough unvaccinated children would be prohibitively time-consuming and difficult.

Second, such a study would also need to account for the many confounding variables that separate some populations from the average U.S. child, including lifestyle factors and genetic variables. To be useful, a comparison would require children matched by age; sex; geographic location; rural, urban, or suburban setting; socioeconomic group; and race/ethnicity.

The committee acknowledges that large-scale, long-term studies of infants through adulthood would be informative for evaluating health outcomes associated with immunization. A new research initiative, the National Children's Study, is a multicenter, congressionally funded effort that meets these criteria. Although such studies would be the optimal design for evaluating long-term health outcomes associated with the childhood immunization schedule, they would require considerable time and funding, and the committee did not find adequate epidemiological evidence to recommend investment in this type of research at this time.

### Secondary Analyses of Existing Data

The most feasible approach to studying the safety of the childhood immunization schedule is through analyses of data obtained by VSD. VSD is a collaborative effort between CDC and 9 managed care organizations that maintain a large database of linked data for monitoring immunization safety and studying potential rare and serious adverse events. VSD member sites include data for more than 9 million children and adults receiving vaccinations on a variety of immunization schedules. However, children who are vaccinated on alternative schedules (including those who are not vaccinated) may differ in meaningful ways. Although this confounding can be minimized through matching and controlling for variations, differences in nonrandomly constructed cohorts cannot be fully accounted for by the use of these data.

The committee discussed several potential modifications that could be introduced into this system that would enable new analyses of the key research questions (Box S-2), including collection of additional data on the participants. The committee found that secondary analyses within VSD would advance knowledge of the safety of the immunization schedule and identified enhancements to improve the data in VSD.

### Animal Models

The committee also reviewed the potential for animal studies to be used to study the childhood immunization schedule. Given the committee's recognition of the complexity of the immunization schedule, the importance of family history, the role of individual immunologic factors, and the complex interaction of the immunization schedule with the health care system, the committee determined that it was more appropriate to focus future research efforts on human research.

### Population Impacts of Alternative Schedules

The committee agreed that evaluations of the recommended immunization schedule need to be attentive to effects at the population level as well as the individual level. Attempts to quantify the relative safety of contrasting immunization schedules need to take into account at least two separate health outcomes: adverse events after the administration of specific vaccines and the overall immunization schedule, and the respective impacts of alternative schedules on the circulation of vaccine-preventable diseases and the consequent adverse outcomes associated with infection.

The intimate association between immunization and age-specific disease incidence needs to be addressed. Specifically, any changes in the immu-

nization schedule that lead to an increase in exposure to preventable disease will increase the spread of the pathogens responsible for these diseases. The population-level impacts of such an outcome would be a simultaneous rise in the incidence of infectious diseases and a reduction in the age at which these illnesses are contracted. Thus, not only is the risk of exposure to preventable diseases increased, but the severity of infection, which is age dependent, is also likely to increase.

## CONCLUSIONS ABOUT STAKEHOLDER CONCERNS

The committee identified concerns among some parents about the number, frequency, and timing of immunizations in the overall immunization schedule. These concerns were not expressed by clinicians, public health personnel, or policy makers in the committee's review. Among the last three groups, the childhood immunization schedule is considered one of the most effective and safest public health interventions available to prevent serious disease and death. Furthermore, the committee's review of the literature did not find high quality evidence supporting safety concerns about the immunization schedule.

In its role to ensure vaccine safety, the federal government has emphasized the engagement of stakeholders in multiple activities. However, an effective national vaccine program will require a more complete and systematic collection of information about stakeholder concerns about vaccine safety, the severity of vaccine-preventable diseases, individual- and population-level immunization rates, the efficacy of immunization, and the delivery and supply of vaccines recommended in the childhood immunization schedule.

To more effectively implement immunization programs, a robust communication and engagement strategy that includes careful study of safety concerns is needed. Currently, the designs used in most studies of immunizations do not permit a detailed analysis of the impact of parental concerns on the decision to immunize their children. Most concerns about safety are expressed by parents, but multiple stakeholders should be included in NVPO efforts. For example, even health care providers with much knowledge about individual vaccines may have less information about the effects of administering multiple vaccines at a single visit or the timing of the immunizations.

**Recommendation 4-1:** The committee recommends that the National Vaccine Program Office systematically collect and assess evidence regarding public confidence in and concerns about the entire childhood immunization schedule, with the goal to improve communication with

health care professionals, and between health care professionals and the public regarding the safety of the schedule.

### CONCLUSIONS ABOUT SCIENTIFIC FINDINGS

The committee encountered two major issues in its review of the findings in the scientific literature. First, the concept of the immunization “schedule” is not well developed. Most vaccine-related research focuses on the outcomes of single immunizations or combinations of vaccines administered at a single visit. Although each new vaccine is evaluated in the context of the overall immunization schedule that existed at the time of review of that vaccine, elements of the schedule are not evaluated once it is adjusted to accommodate a new vaccine. Thus, key elements of the entire schedule—the number, frequency, timing, order, and age at administration of vaccines—have not been systematically examined in research studies.

The second major issue that the committee encountered was uncertainty over whether the scientific literature has addressed all health outcomes and safety concerns. The committee could not tell whether its list was complete or whether a more comprehensive system of surveillance might have been able to identify other outcomes of potential significance to vaccine safety. In addition, the conditions of concern to some stakeholders, such as immunologic, neurologic, and developmental problems, are illnesses and conditions for which etiologies, in general, are not well understood.

Finally, the committee found that evidence assessing outcomes in subpopulations of children who may be potentially susceptible to adverse reactions to vaccines (such as children with a family history of autoimmune disease or allergies or children born prematurely) was limited and is characterized by uncertainty about the definition of populations of interest and definitions of exposures and outcomes.

In summary, to consider whether and how to study the safety and health outcomes of the entire childhood immunization schedule, the field needs valid and accepted metrics of the entire schedule (the “exposure”) and clearer definitions of health outcomes linked to stakeholder concerns (the “outcomes”) in rigorous research that will ensure validity and generalizability.

**Recommendation 5-1:** To improve the utility of studies of the entire childhood immunization schedule, the committee recommends that the National Vaccine Program Office develop a framework that clarifies and standardizes definitions of

- key elements of the schedule,
- relevant health outcomes, and
- populations that are potentially susceptible to adverse events.

## CONCLUSIONS ABOUT RESEARCH METHODS

Vaccine safety is critically important, but a determination of safety is ultimately a value judgment. For example, some might believe that a serious adverse event that occurs once in 1 million doses is “safe enough” relative to the benefit of preventing a serious disease, whereas others may consider that risk unacceptably high. The committee did not set a specific numerical target or goal for what should be considered “safe enough.” Instead, based on the literature, the committee made a judgment that failed to link adverse effects to schedule exposures or multiple immunizations, concluding that there is no evidence that the schedule is not safe.

The committee identified four broad research questions of interest to stakeholders (Box S-2) and discussed general research approaches that could be used to address these questions. Setting of priorities for research will be challenging. The committee proposes a process for setting research priorities that incorporates epidemiological and other evidence (formal systematic reviews), biological plausibility, feasibility, and stakeholder concerns. Before HHS agencies, such as CDC, FDA, the National Institutes of Health, and NVPO, initiate further research on the entire immunization schedule, a thorough review of the biological plausibility of the association of a particular outcome with an aspect of the immunization schedule should be conducted.

**Recommendation 6-1:** The committee recommends that the Department of Health and Human Services incorporate study of the safety of the overall childhood immunization schedule into its processes for setting priorities for research, recognizing stakeholder concerns, and establishing the priorities on the basis of epidemiological evidence, biological plausibility, and feasibility.

The decision to initiate further studies should depend on the evaluation of three considerations that the committee identified through its review of stakeholder concerns and scientific findings:

1. epidemiological evidence of potential adverse health outcomes associated with elements of the immunization schedule (such as postmarketing signals or indications of an elevated risk from observational studies);
2. biological plausibility supporting hypotheses linking specific aspects of the immunization schedule with particular adverse health outcomes; and
3. expressed stakeholder concerns about the immunization schedule’s safety, which should initiate efforts to explore the previous two considerations.

The committee acknowledges the evidence that reduced immunization coverage is associated with increases in the incidence of vaccine-preventable disease and found inconsistent and anecdotal evidence to imply that the recommended immunization schedule is not safe. Moreover, existing adverse event detection systems provide confidence that the existing childhood immunization schedule is safe, and the committee recognizes that the federal government invests considerable resources to ensure vaccine safety. However, some stakeholders have suggested that further research is warranted, such as a comparison of vaccinated children with unvaccinated children or children immunized on alternative schedules.

It is possible to make this comparison through analyses of patient information contained in large databases such as VSD, but it would be unethical and infeasible to conduct an RCT, as summarized above and detailed in Chapter 6. Because an RCT would increase the risk of preventable diseases in individuals and in the community and entail significant amounts of time, money, and other resources, the committee concludes that new RCTs of the childhood immunization schedule are not justified at this time.

**Recommendation 6-2: The Department of Health and Human Services should refrain from initiating randomized controlled trials of the childhood immunization schedule that compare safety outcomes in fully vaccinated children with those in unvaccinated children or those vaccinated by use of an alternative schedule.**

The committee concludes that secondary analyses of existing data are more promising approaches to examination of the research questions identified by the committee in future studies of the childhood immunization schedule. VSD is a useful collaborative project for conducting both postmarketing surveillance and longer-term targeted research. The ability to augment the routinely collected administrative data in VSD with parent interviews and reviews of medical records for selected study populations is an important strength.

VSD is currently the best available system for studying the safety of the immunization schedule in the United States. VSD should strive to improve its generalizability to the U.S. population by enhancing the quality of its demographic information or by expanding its scope to include more diversity in its study populations. Secondary analyses with data from other existing databases could also be feasible, ethical, and cost-effective in investigating several of the research questions that the committee identified.

The committee recognizes that the currently funded managed care organizations' commitment to VSD studies needs to remain high to continue and build on existing efforts. The committee concludes that VSD is a valuable component of the federal research infrastructure and will be the best-suited source of data for studying the childhood immunization schedule. VSD's



utility will be expanded with the addition of more detailed demographic data and family medical histories.

**Recommendation 6-3:** The committee recommends that the Department of Health and Human Services (HHS) and its partners continue to fund and support the Vaccine Safety Datalink project to study the safety of the recommended immunization schedule. Furthermore, HHS should consider expanding the collaboration with new health plan members and enhancing the data to improve its utility and generalizability.

### CONCLUDING OBSERVATIONS

The committee's efforts to identify priorities for recommended research studies did not reveal an evidence base suggesting that the childhood immunization schedule is linked to autoimmune diseases, asthma, hypersensitivity, seizures, child developmental disorders, learning disorders or developmental disorders, or attention deficit or disruptive behavior disorders. Although stakeholder concerns should be one of the elements used to drive searches for scientific evidence, these concerns alone, absent epidemiological or biological evidence, do not warrant the initiation of high-cost research studies. The committee concludes that the use of existing data from database systems to conduct observational studies offers the best means for ongoing research efforts about the immunization schedule's safety.

The committee found no significant evidence to imply that the recommended immunization schedule is not safe. Furthermore, existing surveillance and response systems have identified known adverse events associated with vaccination. The federal research infrastructure is a strong system. A key component is the VSD project, which with ongoing support will be able to feasibly address the committee's research questions identified in Box S-2. Although the committee concluded that protecting children from vaccine-preventable diseases is of higher importance than testing alternative immunization schedules without epidemiological or biological evidence indicating a safety problem, VSD should continue to examine the health outcomes of people who choose alternative schedules.

Looking to the future, the committee supports the work of the federal research infrastructure to ensure that stakeholders are involved in all stages of the development, implementation, evaluation, and dissemination of the immunization schedule. As electronic medical records become more commonly used, they may provide an opportunity to capture complete immunization data linked with hospital discharge records, which will be useful to future studies. Newer initiatives such as the National Children's Study



*SUMMARY*

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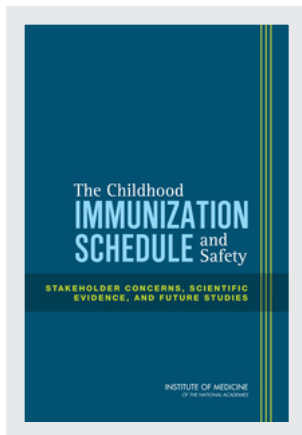
and the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program also hold promise in providing further study opportunities.

The childhood immunization schedule may become more complex over time as scientific advances are made and new vaccines are developed and incorporated into the schedule. Feasible research approaches to study potential adverse health outcomes will emerge only with sustained and substantial federal commitment to research on vaccine safety.

# **EXHIBIT 288**

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## The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies (2013)

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## 4

## Stakeholder Concerns Related to the Safety of the Immunization Schedule

Immunizations represent a unique health intervention because they simultaneously affect the health of individuals and the health of their communities. The success of vaccination programs in reducing the human reservoir of infectious diseases requires the collaboration and participation of a complex system of stakeholders in which each plays a specific role. These stakeholders include but are not limited to the parents of children who receive vaccines, the physicians and other health care professionals who deliver inoculations, and public health professionals who ensure vaccine delivery and safety. The concerns that surround the immunization schedule are equally complex and diverse.

Concerns about vaccines have historically had a significant impact on the immunization system. Decreases in measles, mumps, and rubella (MMR) vaccine coverage in the United Kingdom are largely attributed to parental fears of autism linked to immunization with MMR following publication of the discredited Wakefield paper, which falsely claimed to demonstrate this association and was subsequently retracted years later by *Lancet* (Brown et al., 2012; Madsen and Vestergard, 2004; Taylor et al., 1999). In the 1970s, concerns about adverse effects from the whole-cell pertussis vaccine contributed to a decrease in uptake and halted pertussis vaccination programs in some countries. From this controversy came innovation that created the acellular pertussis vaccine, which has fewer observed adverse effects, as well as policy changes in the United States with the enactment of the National Childhood Vaccine Injury Act (IOM, 1992; Noble et al., 1987).

The committee recognized the challenge and importance of identifying

and understanding the range of stakeholder concerns about the childhood immunization schedule and its safety. To gain a fuller understanding of this system, the committee developed a strategy to gather and analyze stakeholder concerns, which included a review of the existing literature, listening to public testimony, and soliciting comments on a commissioned paper.

## IDENTIFICATION OF STAKEHOLDERS

Given the committee's charge, the first step was to identify stakeholders whose concerns focused on the safety of the immunization schedule rather than the safety of individual vaccines or nonsafety issues such as cost or convenience. To begin, the committee consulted the list of stakeholders from the 2008 Institute of Medicine (IOM) report *Initial Guidance for an Update of the National Vaccine Plan: A Letter Report to the National Vaccine Program Office* (IOM, 2008), which is also referenced in the 2010 National Vaccine Plan of the U.S. Department of Health and Human Services. As a second step, the committee categorized the extensive list of stakeholders by their general interest in immunization (Box 4-1).

### BOX 4-1 Stakeholders in the U.S. National Vaccine System

- Academic researchers
- Advocacy groups
- Federal government agencies, departments, and federal advisory committees
- General public (including parents)
- Health care system and providers
- International organizations
- Media
- Nongovernmental organizations
- Philanthropic organizations
- State, local, and tribal governments and public health agencies
- Travel industry
- Vaccine distributors
- Vaccine industry
- Vaccine investors

SOURCES: IOM (2008) and adapted from the 2010 National Vaccine Plan ([http://www.hhs.gov/nvpo/vacc\\_plan/2010\\_percent20Plan/appendix5.pdf](http://www.hhs.gov/nvpo/vacc_plan/2010_percent20Plan/appendix5.pdf)).

## INFORMATION GATHERING

After identifying key stakeholders, the committee reviewed the most frequently expressed concerns related to the safety of the immunization schedule from three primary sources of information: the current literature, online postings, and public testimony.

The committee reviewed all the information that interest groups, individuals, and researchers provided through the online submissions and in public testimony at the committee meetings and throughout the study period. Even before the first committee meeting, the committee received online testimony as well as many e-mail messages. The committee held three public meetings that included information-gathering sessions and a session during which it heard public testimony. During the three public meetings, the final hour was reserved for stakeholders to share their concerns related to the committee's charge. Throughout the study, the committee also reviewed media coverage and scientific articles related to the safety of the immunization schedule. However, the committee based its review of the safety of the immunization schedule on information reported in the scientific literature.

The literature review focused on the recommended childhood immunization schedule and yielded an extensive body of scientific articles, reports in the popular media, reviews, and summaries. Because the committee's study period was limited (no longer than 12 months), the committee established priorities to identify and review the most common and noteworthy stakeholder concerns about the safety of the childhood immunization schedule.

## LITERATURE SEARCH

The committee used the Ovid MEDLINE database to search the scientific literature published within the past 10 years (2002 to 2012). Multiple comprehensive searches were used to identify references that described stakeholder concerns and analyzed health outcomes after immunization according to the recommended childhood immunization schedule. The committee focused on articles published in the past 10 years because the childhood immunization schedule has been modified several times as new vaccines have been approved and incorporated into the schedule. Concerns related to the 2001 recommended childhood immunization schedule are likely to be different from concerns related to 2012's schedule, which recommends additional immunizations for children. Because the committee's task was to assess the safety of the immunization schedule rather than the safety of individual vaccines, the literature searches did not include articles that focused on a single vaccine. The committee's review included peer-reviewed publications such as scientific articles, reviews, commentaries,

and editorials. The committee used medical subject heading searches to identify references, using the terms “immunization” (which includes “immunization schedule”), “vaccines,” “attitude to health,” and “attitude of health personnel.”

The initial literature search yielded 421 articles. To further refine the search, the committee reviewed the titles and abstracts (when available) and removed articles that met any of following three exclusionary criteria. First, from the beginning of the study period, the committee noted that the childhood immunization schedule spans the entire period of childhood (birth to age 18 years). The committee found that the most prominent safety concerns about the immunization schedule are related to vaccinations received during infancy and early childhood. Thus, the committee focused its review on the body of literature that addressed concerns about the short- and long-term effects of the schedule of vaccinations given to young children (birth to age 6 years) and excluded studies that focused on the immunization schedule for older children and adolescents (age >6 years). Second, the committee excluded studies that focused on individual vaccines or combination immunizations rather than the entire childhood immunization schedule. Finally, the committee excluded studies of non-U.S. populations, unless the study focused on the U.S. Advisory Committee on Immunization Practices (ACIP)–recommended immunization schedule for young children.

After the committee applied these criteria, it retained 85 published articles for comprehensive review. Two-thirds of these articles were categorized as studies of parental concerns about either safety ( $n = 26$ ) or communication between providers, public health authorities, and parents ( $n = 31$ ). Several articles that the committee reviewed did not meet the study criteria (largely owing to having an older publication date) but were frequently cited in the literature and added to the committee’s knowledge base.

An iterative review of the literature as well as oral and written public comments revealed that among the primary stakeholders (parents, health care providers, public health officials), a subset of parents were the group with the most concerns about the safety of the immunization schedule. The review also revealed that parents, providers, and public health officials all believe that effective communication about these safety concerns remains a challenge.

## PARENTAL CONCERNS IN THE SCIENTIFIC LITERATURE

Parental concerns about the safety of vaccines and the immunization schedule have been well publicized but are not well understood by all health care professionals. A number of recent studies have described the challenges associated with research into the safety of the immunization schedule and defined the methods that can be used to elicit and quantify parental con-



cerns (Dempsey et al., 2011; Freed et al., 2010; Gust et al., 2005; Kennedy et al., 2011a; Niederhauser et al., 2001; Salmon et al., 2004).

In 2000, Gellin et al. reported that the two most common concerns that parents expressed about childhood immunizations were that too many vaccines were being administered to infants and children and that childhood vaccines may weaken the immune system (Gellin et al., 2000). The 2002 IOM report *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* determined that no biological or epidemiological evidence for such concerns was available and that infants receive more antigenic exposures from the natural world, including exposures to infections for which no vaccine is provided. The report noted, however, that “the committee concludes that concern about multiple immunizations has been, and could continue to be, of societal significance in terms of parental worries, potential health burdens, and further challenges for immunization policy-making” (IOM, 2002, p. 12)

A recent study of the concerns stated by parents with young children (<7 years) in the 2010 HealthStyles survey revealed a number of vaccine-related attitudes and concerns (Kennedy et al., 2011b). The concerns that 376 respondents reported the most frequently are listed in Table 4-1.

Similar results were found in the 2002 HealthStyles and ConsumerStyles surveys of a nationally representative sample of 697 parents, although the rank order of their concerns was slightly different (Gust et al., 2005). Despite documented parental concerns about vaccines, most parents still have their children receive the recommended immunizations. In fact, the 2010 National Immunization Survey (NIS) reported that less than 1 percent of toddlers had received no vaccines at all (CDC, 2012).

A 2011 article focused on the relationship between parents’ attitudes toward childhood immunizations and the decision to delay or decline immunizations (Smith et al., 2011). Using data from the 2009 NIS, the researchers reviewed 11,206 parents’ reports of immunization delays and refusals. Approximately 60 percent of parents with children aged 24 to 35 months neither delayed nor refused immunizations; 26 percent only delayed

**TABLE 4-1** Vaccine-Related Concerns, 2010

Vaccine-Related Concern	Percentage of Responses
It is painful for children to receive so many shots during one doctor’s visit.	38
My child is getting too many vaccines in one doctor’s visit.	36
Children get too many vaccines during the first 2 years of life.	34

SOURCE: Kennedy et al., 2011b.

one or more immunizations; 8 percent refused one or more immunizations; and approximately 6 percent both delayed and refused one or more immunizations. Concerns were aggregated into categories such as a lack of trust that vaccines are safe, suspicions that vaccines might produce serious side effects, concerns that too many vaccines can overwhelm a child's immune system, and the general sense that their children are immunized with too many vaccines (Smith et al., 2011).

Safety concerns have led some parents to prefer alternative immunization schedules that may involve delaying specific immunizations or omitting some or all immunizations. A recent review of the literature on the growing trend of following alternative immunization schedules produced a summary of parental concerns, such as concerns about vaccine safety, efficacy, and necessity; distrust of vaccine advocates' motivation; and insufficient information with which to make an informed decision (Dempsey et al., 2011). Health care providers reported that parents' requests for an alternative schedule may be based on a specific immunization schedule or may reflect parental concerns about an individual vaccine rather than the entire schedule.

A recent cross-sectional, Internet-based survey of a representative sample of parents of young children (ages 6 months to 6 years) reported that less than 10 percent of parents indicated that they follow an alternative immunization schedule (Dempsey et al., 2011). The study identified the four vaccines that were the most commonly refused: the H1N1 influenza, seasonal influenza, rotavirus, and varicella vaccines. In general, newer vaccines were more likely to be declined than were established vaccines. Parents who requested a delay for a specific vaccine most commonly (more than 40 percent) requested a delay in receiving MMR and the varicella vaccine.

In 2009, Freed et al. conducted an online survey and reported that the varicella and meningococcal vaccines were the most commonly refused (Freed et al., 2009). An analysis of responses to the NIS in 2003 and 2004 also reported that the varicella vaccine was the one that prompted the most concerns among parents who declined immunizations for their children (Gust et al., 2008).

Although parents have various reasons for declining or delaying immunizations, a 2011 study also reported that a large proportion of parents who requested an alternative immunization schedule understood and acknowledged that undervaccination increases the risk of infection and spread of disease in the community (Dempsey et al., 2011). Despite recent increases in the popularity of alternative immunization schedules, their use remains infrequent (Dempsey et al., 2011; Robison et al., 2012).

Analysis of the data from the 2003-2004 NIS revealed that parents of underimmunized children articulated their concerns about the safety of the immunization schedule in the popular media more forcefully than did

parents of fully immunized children (Gust et al., 2004). Results of a later iteration of the 2009 NIS found that parents of fully immunized children reported concerns about vaccines, but their concerns did not preclude immunization of their children (Kennedy et al., 2011a).

In their public testimony during the committee meetings, parents provided a range of concerns about the immunization schedule; the committee received limited public testimony from parents who endorse the recommended schedule, despite evidence that the majority of U.S. parents support and follow ACIP's recommendations (CDC, 2012).

The 2004 NIS reported that parental concerns about vaccine safety were associated with underimmunization, which is further associated with adverse health outcomes for individuals and their communities, including increases in the prevalence of vaccine-preventable diseases (Gust et al., 2004). Furthermore, the designs used in most studies of immunizations do not permit a detailed analysis of the impact of parental concerns on parents' decision to immunize their children (Kennedy et al., 2011b). And, although many research studies have focused on parental concerns about vaccine safety, they have not adequately explored parental knowledge of the protective benefits of immunizations.

The committee identified a need for further study of parental attitudes and concerns about immunization. Based on the committee's review of the literature and public testimony, the committee strongly endorses research to understand parents' knowledge, beliefs, and concerns about vaccines and vaccine-preventable diseases, which is a key component of the 2010 National Vaccine Plan.

## PUBLIC CONCERNS PRESENTED TO THE COMMITTEE

The public testimony presented to the committee highlighted concerns about the quality and strength of existing research on vaccine safety in the United States. Some individuals who provided public testimony focused on the lack of research on vaccine safety for subpopulations that may be potentially susceptible to adverse events. For example, children with family histories of adverse vaccine events, autoimmune diseases, allergies, and neurological diseases were described to be underrepresented in prelicensure and clinical trials of childhood immunizations.

Furthermore, public testimony to the committee described the speculation that children with a family history of autoimmune disease or allergies and premature infants may be additional subpopulations at increased risk for adverse effects from immunizations. The 2012 IOM report *Adverse Effects of Vaccines: Evidence and Causality* supports the fact that individuals with certain characteristics (such as acquired or genetic immunodeficiency)

are more likely to suffer adverse effects from particular immunizations, such as MMR and the varicella vaccine (IOM, 2012).

During each of the three public sessions held in conjunction with committee meetings, the testimony of many individuals and organizational representatives revealed a lack of trust in the quality and thoroughness of vaccine safety research. Several individuals recommended that the committee review the scientific studies that have compared health outcomes among fully vaccinated, partially vaccinated, and unvaccinated children as well as children who have been vaccinated according to alternative schedules.

The comments that were submitted through an online questionnaire in response to the committee's commissioned paper (see Appendix D) echoed many of the concerns and suggestions that were articulated during the three public sessions. The sentiments largely focused on the concern that the recommended immunization schedule bombards children's immune systems with an excessive number of antigens at an early age and may not be as safe as possible.

### PATIENT-PROVIDER COMMUNICATION

As indicated by the high rates of vaccination coverage, most American parents believe that vaccinations are an effective way to protect their children from serious infectious diseases (CDC, 2012). Despite this strong support, parents have concerns, questions, and misperceptions about childhood immunizations (Kennedy et al., 2011b). Parents seek information about vaccine safety from a multitude of sources: public health authorities, pediatricians, other child health care professionals, professional organizations' websites, personal blogs, celebrities, and advocacy groups (Freed et al., 2011).

With such a wide range of sources of information about immunizations, the committee recognized the likelihood that parents could receive conflicting information that could exacerbate their concerns and confusion about the safety of vaccines. The committee also noted the many high-quality websites and materials that have recently been produced, including Vaccines.gov and materials produced by the American Academy of Pediatrics (AAP) and available on the AAP website. However, findings from an online survey conducted as part of an ongoing study of 2,521 parents and nonparents demonstrated that although websites from doctors' groups, such as AAP, and government websites were trusted by the greatest proportion of surveyed parents (27 and 7 percent, respectively), a larger proportion did not view or use these resources at all (29 and 38 percent, respectively) (Freed et al., 2011).

Apart from the confusion associated with conflicting sources of information about childhood vaccines (Freed et al., 2011), the committee's

review of the scientific literature and the public testimony identified the lack of parental trust in vaccines and vaccine safety to be an important concern. Overall, a large majority of parents rely on the professional advice they receive from their child's doctor or health care provider, and they report high levels of trust in their doctor's advice (Freed et al., 2011). However, a recent study reported that 26 percent of parents trusted celebrities as a reliable source of information on the safety of vaccines (Freed et al., 2011). Thus, although the relationship between the parent and the child's health care provider is a strong determinant of decision making about childhood vaccines, some parents rely on nonprofessional sources of information to make the same decisions (Gust et al., 2008; Serpell and Green, 2006).

In some cases, pediatricians may dismiss parents from their practice if the parents decline vaccines, delay vaccinations, or base their decisions on unscientific information (Flanagan-Klygis et al., 2005). For example, a 2011 study reported that more than 30 percent of Connecticut pediatricians have dismissed families because of their refusal to immunize their children (Leib et al., 2011). AAP discourages the dismissal of parents on the basis of their refusal to immunize their children (Diekema and the AAP Committee on Bioethics, 2005). Furthermore, AAP believes that providers should maintain a relationship with families that decline immunizations so that children continue to receive appropriate medical care. In addition to the value of that care, the continuing relationship provides an opportunity for the pediatrician to encourage parents to consider immunization of their children in the future (Diekema and the AAP Committee on Bioethics, 2005). The committee also notes that the dismissal of families from pediatric practices could further erode trust in the health care system.

A recent study of 209 pediatricians in Washington State reported that parental requests for alternative immunization schedules are not uncommon (Wightman et al., 2011). Overall, 61 percent of these pediatricians agreed that they were comfortable using different schedules if the parents made this request. The three vaccines that most pediatricians were willing to delay were the hepatitis B vaccine (69 percent), varicella vaccine (53 percent), and inactivated poliovirus vaccine (45 percent) (Wightman et al., 2011).

Based on the literature review and public testimony, the committee noted the importance of providers' knowledge of vaccine safety. Furthermore, the committee found it to be essential that providers use a communication style that elicits parents' concerns and encourages respectful dialogue to address divergent opinions. Even though health care providers may focus on the benefits of childhood immunizations, they may not adequately discuss the anticipated, higher-prevalence side effects or the potential events that are significantly more rare and severe. Therefore, based on the review of the scientific literature and the public input, the committee believes that



all health care providers who immunize children should receive training in communication with the goal of improving provider-parent communication of immunization issues (Gust et al., 2008a).

Apart from the need for training in communication, the committee reviewed several recent studies that identified the need for improved communication about vaccine safety by the scientific community and public media (Gust et al., 2006, 2008b; Levi, 2007). Gust et al. (2006) suggested that enhanced communication training for providers should increase their willingness to engage parents in discussions of vaccine and immunization issues.

Studies are also under way to develop techniques to identify categories of vaccine hesitancy and develop tools to assist providers as they communicate with parents who express concerns about vaccines (Diekema, 2012). The 2002 IOM report *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* recommended that an appropriate panel of multidisciplinary experts be convened to “develop a comprehensive research strategy for knowledge leading to the optimal design and evaluation of vaccine risk-benefit communication approaches” (IOM, 2002, p. 16). Furthermore, the 2010 IOM study described in the report *Priorities for the National Vaccine Plan* emphasized that communication must reflect current research and strategies (IOM, 2010).

Government agencies and professional organizations play a key role in providing parents with information on vaccines and immunizations. However, the public erosion of trust in government and the suboptimal effectiveness of public health campaigns on immunizations in particular highlight the challenges of mounting an effective strategy of communication about the childhood immunization schedule. This challenge is exacerbated by the fact that public decision making as it applies to vaccines is driven not only by scientific and economic evidence but also by political, psychological, and sociocultural factors.

## CONCLUSIONS

From the literature review and the comments received online and during the public sessions, the committee determined that although the majority of parents adhere to the ACIP-recommended immunization schedule for their children, many parents remain concerned that their children may face unnecessary risks because of the timing and number of vaccinations.

The decisions that parents make about the risk of disease versus the risk of immunization are attributable, in part, to the significant and sustained declines in most vaccine-preventable diseases that have resulted in the community immunity (also known as herd immunity) that vaccination policy has achieved. Although some parents may not fully understand the

concept of community immunity, at some level, many parents understand that widespread efforts to immunize children protect both vaccinated and unvaccinated children. The protection offered by community immunity may mislead some parents who decline all immunizations and allow them to believe that childhood vaccines are unnecessary, when vaccination in the community has actually shielded their children from serious infectious diseases (Chen et al., 2005). Finally, some parents are concerned about their child's risk of complications of immunization with a vaccine on the basis of family history or the child's medical conditions, and, decide to delay or omit immunizations. Children with certain predispositions are more likely to suffer adverse events from vaccines than are those without that risk factor, such as children with immunodeficiencies who are at increased risk for developing invasive disease from a live virus vaccine (IOM, 2012). The committee recognizes that while the CDC has identified persons who should not be vaccinated because of certain symptoms or conditions, some stakeholders question if that list is complete. Potentially susceptible populations may have an inherited or genetic susceptibility to adverse reactions, and further research in this area is ongoing.

Thus, the committee understands that parental concerns are an expression of concern over and a way to care for their children's health and well-being. However, the committee also recognizes that a growing pattern of delaying or declining all or some vaccines has already contributed to outbreaks of vaccine-preventable diseases and mortality across the United States. These disease outbreaks place children and adults at risk, including children who are only partially immunized or experience waning immunity. Immunized children and adults in the community represent another group of stakeholders, and the committee recognizes the concern about declining community immunity as well.

Research from telephone surveys and other methods reviewed in this chapter typically provide information about what participants think, but such surveys usually cannot probe into why respondents think the way they do. To develop an effective risk-benefit communication strategy, more detailed research is warranted. The committee concludes that parents and health care professionals would benefit from the availability of more comprehensive and detailed information with which to address parental concerns about the safety of the vaccines in the immunization schedule. Such information should clearly address vaccine-preventable diseases, the risks and benefits of immunizations, and the safety of the vaccines in the immunization schedule.

At present, as described in Chapter 5, relatively few studies have directly assessed the immunization schedule. Although health care professionals have a great deal of information about individual vaccines, they have much less information about the effects of immunization with multiple



vaccines at a single visit or the timing of the immunizations. Providers are encouraged to explain to parents how each new vaccine is extensively tested when it is approved for inclusion in the recommended immunization schedule. However, when providers are asked if the entire immunization schedule has been tested to determine if it is the best possible schedule, meaning that it offers the most benefits and the fewest risks, they have very few data on which to base their response. Furthermore, although the 2010 National Vaccine Plan addresses the need to provide health care providers with more timely, accurate, and transparent information about the benefits and risks of vaccines, providers are not singled out in specific strategies offered by the U.S. Department of Health and Human Services.

Although the committee identified several studies that reviewed the outcomes of studies of cumulative immunizations, adjuvants, and preservatives (see Chapter 5), the committee generally found a paucity of information, scientific or otherwise, that addressed the risk of adverse events in association with the complete recommended immunization schedule, even though an extensive literature base about individual vaccines and combination immunizations exists. The committee also acknowledges that the public health community has in place monitoring systems that work very well for the detection of adverse events that occur in the short term after immunization and that could be enhanced for the detection of longer-term outcomes, as discussed in Chapters 3 and 6. The continuation of studies looking at immune phenotyping, such as those of the National Institutes of Health's Human Immunology Project Consortium, is also important in the identification of populations that are potentially susceptible to adverse events (HIPC, 2012).

To achieve the goal of giving health care providers and parents information that addresses the concerns that correlate with delaying or declining childhood immunizations, the committee developed a list of priority areas in which more information or clear communication of existing research is needed. The committee summarizes the priority concerns into the following topics:

1. Immune system overload. As several parents asked, are children given too many vaccines? Do immunizations start when babies are too young? Are immunizations administered too frequently?
2. Immunization schedule. What is the evidence that the ACIP-recommended immunization schedule is better than other schedules? Could the health outcomes among children who are vaccinated according to the recommended schedule be compared with those among unimmunized children? Likewise, could the health outcomes among children vaccinated on the recommended schedule

be compared with those among children vaccinated on alternative schedules?

3. Are subpopulations of children potentially susceptible to adverse reactions to vaccines, such as children with a family history of autoimmune disease or allergies or children born prematurely?

The committee recognizes not only that additional information is needed to address parental concerns but also that other factors will affect parental decision making. For example, in the testimony and online comments, the committee identified skepticism about (1) the quality of vaccine research (prelicensure and postmarketing), (2) the influence of pharmaceutical companies on scientific research, and (3) the influence of the governmental entities that oversee vaccine research. In addition, as stated earlier, clear and effective parent-provider communication is essential to convey accurate information and foster mutual trust.

The committee's review of the determinants of public trust in vaccination campaigns and information on vaccines identified three types of concerns raised by stakeholders:

- knowledge and expertise,
- openness and honesty, and
- concern and care.

Thus, improved communication between public health authorities and parents requires improvements to the clarity of the information and the effectiveness with which the information is conveyed, as well as the building of trust and the use of a systematic approach to elicit public concerns. Further research into the impact of parental perceptions about risk on their decisions about immunizing their children is indicated, and that research should be performed by methods that use decision and social science (Larson et al., 2011).

The committee acknowledges that parents and providers are not the only stakeholders who are concerned about the safety of the immunization schedule. The committee listened to presentations from a range of stakeholders whose concerns focused on providing immunizations to preserve community immunity and to prevent the reemergence of vaccine-preventable diseases, which ultimately requires the cooperation and trust of parents in immunizing their children. These other groups and individuals who also have a vested interest in providing children with a safe and effective immunization schedule include pharmaceutical companies; federal, state, and local governments; health insurers; the many health care providers who oversee administration of vaccines; and many others in the health care system.

The committee also acknowledges that the low rate of many infectious diseases may encourage parents to focus on the risks of immunizations rather than the risk of vaccine-preventable diseases. These low rates of infectious diseases may reinforce parents' reliance on community immunity to protect their child rather than choose immunizations.

The vaccine safety activities of the federal government are prioritizing the engagement of stakeholders in multiple activities, detailed in the 2010 National Vaccine Plan and implementation efforts, as well as the Scientific Agenda of the Centers for Disease Control and Prevention's Immunization Safety Office. However, an effective national vaccine program will require better-quality information on stakeholder concerns about the safety of vaccines, the severity of vaccine-preventable diseases, individual and population-level immunization, vaccine efficacy, and the delivery and supply of vaccines recommended in the childhood immunization schedule. To effectively implement immunization programs, a state-of-the-art communication plan is needed.

**Recommendation 4-1: The committee recommends that the National Vaccine Program Office systematically collect and assess evidence regarding public confidence in and concerns about the entire childhood immunization schedule, with the goal to improve communication with health care professionals, and between health care professionals and the public regarding the safety of the schedule.**

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## STAKEHOLDER CONCERNS

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# **EXHIBIT 289**

# Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality (1994)

## Chapter: 1 Executive Summary

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### 1

## Executive Summary

"Our aim, therefore, must be to study these [complications] as fully as possible in the confident expectation that, as in other branches of science, knowledge will bring enlightenment" (Wilson, 1967).

Childhood immunization has been one of the foremost public health measures of the twentieth century. It has allowed control and prevention of many diseases from which morbidity and mortality can be staggering. Medical personnel in the United States currently rarely see a case of the infectious diseases against which the vaccines are directed. Yet, recent measles epidemics on college campuses and in inner cities suggest that vaccine-preventable disease is not to be ignored. The first health initiative of the immunization programs to boost vaccination rates in the United States, particularly for children under age 2 years.

## BACKGROUND AND HISTORY

The public policy debate regarding immunization stretches beyond the question of how to meet the goals of universal immunization. Concern over the safety of pertussis vaccine was long-standing in Great Britain by the time of the 1982 airing in the United States of a documentary entitled "DPT: A Shot in the Dark" (Coulter and Fisher, 1985). Concern has stretched to other vaccines and has spawned the formation of groups of interested citizens throughout the United States, for example, National Vaccine Information Center/Dissatisfied Parents Together, Determined Parents to Stop Hurting Our Tots, Concerned Health Professionals and Others, and Parents

Concerned About the Safety of Vaccines. More articles and books have been published (e.g., Counter, 1990; Miller, 1992) to alert the public to the potential risks of vaccination.

In 1986, the US. Congress passed the National Childhood Vaccine Injury Act (NCVIA; P.L. 99-660) in response to worries about the safety of currently licensed childhood vaccines and in response to the economic pressures that were threatening the integrity of childhood immunization programs. The litigation costs associated with claims of damage from vaccines had forced several companies to end their vaccine research and development programs as well as to stop producing already licensed vaccines. The NCVIA was an attempt to encourage and ensure vaccine production by creating a no-fault compensation program (the National Vaccine Injury Compensation Program) as a required first resort for those who believed that they or their children had been injured by certain vaccines. The need for a compensation program had long been recognized,



and several groups have proposed possible mechanisms for compensating people believed to be injured by vaccination (Institute of Medicine, 1985; Office of Technology Assessment, 1980). This program was envisioned to alleviate, but not completely eliminate, manufacturer liability and encourage research and development of more and safer vaccines. The compensation program is administered by the federal government and is financed by an excise tax on the sale of vaccines covered by the program (Iglehart, 1987; Mariner, 1992).

In addition to establishing the compensation program, the NCVIA set forth other vaccine-related efforts to be carried out by the U.S. Department of Health and Human Services, including mandatory reporting of specific adverse events following childhood immunizations against diphtheria, tetanus, pertussis, measles, mumps, rubella, and polio (see box entitled The Vaccine Injury Table in [Chapter 10](#)); voluntary reporting of any reaction to any immunization to the Vaccine Adverse Event Reporting System (see [Chapter 10](#) for a discussion of this passive surveillance system and [Figure B-1](#) for a copy of the reporting form); the creation of a National Vaccine Program Office to coordinate federal vaccine initiatives and to help meet immunization coverage goals; the establishment of advisory groups to the National Vaccine Program and the National Vaccine Injury Compensation Program; and better communication of the potential risks of vaccines through public information pamphlets that are distributed at the time of vaccination (under the direction of the Centers for Disease Control and Prevention) and changes in vaccine package inserts (under the direction of the U.S. Food and Drug Administration).

The NCVIA also mandated that the Secretary of the U.S. Department of Health and Human Services enlist the help of the Institute of Medicine (IOM) of the National Academy of Sciences to study the adverse effects of childhood vaccines. The NCVIA called for two specific studies. The first,

mandated under Section 312 of P.L. 99-660, was to address the serious adverse effects of pertussis and rubella vaccines. The Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines published its findings in 1991 (Institute of Medicine, 1991). Appendix A contains the Executive Summary of that report.

The second study, mandated under Section 313 of P.L. 99-660, was to review adverse events associated with other vaccines commonly administered during childhood. The Vaccine Safety Committee, which was charged with performing the second study, was convened early in 1992. The results of that inquiry are provided in this report.

## THE CHARGE TO THE COMMITTEE

The members of the interdisciplinary, 14-member Vaccine Safety Committee have expertise in such areas as immunology, pediatrics, internal medicine, infectious diseases, neurology, virology, microbiology, epidemiology, and public health. The committee was charged with (1) reviewing the relevant scientific and medical literature on specific risks to children associated with the vaccines or vaccine components directed against tetanus, diphtheria, measles, mumps, polio, *Haemophilus influenzae* type b, and hepatitis B currently licensed for use in the United States and (2) reviewing the available data on specific risk-modifying factors, that is, circumstances under which administration of these vaccines increases the risk of an adverse event, characteristics of groups known to be at increased risk of an adverse event, and timing of vaccination that increases the risk of an adverse event.

Risk-benefit comparisons or recommendations about immunization schedules were not within the charge to the Vaccine Safety Committee. Despite the name of the committee, many aspects of vaccine safety, such as purity standards or production techniques, also were beyond the committee's charge.

Both IOM studies and the P.L. 99-660 committee had the evaluation of the weight of scientific and medical evidence bearing on the question of whether a causal relation exists between certain vaccines and specific serious adverse events. Like the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines, the Vaccine Safety Committee approached its task from a position of neutrality, presuming neither the presence nor the absence of a causal relation between the vaccines and the adverse events under consideration.

## THE STUDY PROCESS

Over the course of 18 months, the committee met six times, reviewed more than 7,000 abstracts of scientific and medical studies, read more than 2,000 published books and articles (including many sources in the non-

English literature), analyzed information from U.S. Public Health Service-administered reporting systems for adverse reactions to vaccines, and considered material submitted by interested parties. The committee solicited input from scientists who were invited to participate in two open scientific meetings and from other interested parties at two open public meetings. Details regarding how the committee gathered information are given in [Appendix B](#). All salient information from those reviews is contained in this report.

P.L. 99-660 stated that the review was to include those vaccines covered by the National Vaccine Injury Compensation Program. *Haemophilus influenzae* type b (Hib) and hepatitis B vaccines were added for consideration because of the increasing use of these vaccines and the supposition that in the near future they could be mandatory vaccines covered by the National Vaccine Injury Compensation Program. The list of adverse events investigated for this report derived primarily from negotiations with representatives of the U.S. Public Health Service. However, preliminary investigations into additional adverse events were prompted by queries from interested parties or committee members. After considering the information from these preliminary investigations, the committee added several vaccine-adverse event relations to the original list. [Table B-1 in Appendix B](#) contains a complete listing of the specific vaccine-adverse event relations under study.

The report begins with background information. [Chapter 2](#) contains an in-depth discussion of the approach used by the committee to weight the evidence and assess causality. Information on the neurologic disorders and immunologic reactions discussed in much of the report is contained in [Chapters 3 and 4](#). [Chapters 5 through 9](#) include the vaccine-specific evidence and conclusions. All information (evidence, causality argument, and conclusions) regarding death as an adverse event associated with vaccination is contained in [Chapter 10](#).

*Adverse Effects of Pertussis and Rubella Vaccines* (Institute of Medicine, 1991), the report of the predecessor IOM committee, provides an in-depth review of the literature concerning the adverse events associated with diphtheria and tetanus toxoids and pertussis vaccine (DPT), as well as pertussis vaccine, and should be referred to for conclusions regarding DPT. [Appendix A](#) contains the Executive Summary of that report. The charge to the Vaccine Safety Committee was to examine adverse events associated with tetanus toxoid as well as tetanus and diphtheria toxoid combination preparations. The committee reviewed data concerning DPT if the data also concerned diphtheria and tetanus toxoids for pediatric use (DT); however, it was beyond the committee's scope to make conclusions about pertussis vaccine or DPT.

The IOM Committee to Review the Adverse Consequences of Pertussis

and Rubella Vaccines made determinations of causality only for rubella vaccine and the rubella vaccine component of multivalent vaccines, but not for measles-mumps-rubella vaccine (MMR). Thus, the Vaccine Safety Committee reviewed data regarding immunization with MMR as well as data on monovalent measles and mumps preparations. The committee has made separate determinations of causality for the measles and mumps vaccine components for the adverse events for which data were available, particularly if measles or mumps vaccine-strain virus was isolated from the patient. In circumstances in which a causality assessment specific to monovalent measles or mumps vaccine was not possible, this is stated in the conclusion regarding that specific adverse event.

In circumstances in which the committee determined that a component of a multivalent preparation was causally related to a specific adverse event, but there is no direct experience of such an adverse event being caused by the multivalent preparation, the committee states this, but judges that the combined preparation also is causally related to that adverse event.

Many case reports described an adverse event(s) in a patient who received more than one vaccine. A common combination, as a result of the immunization schedules recommended in the United States, is DPT, oral polio vaccine, and Hib vaccine. Assessment of causality in those reports was more difficult than if the patient had received only one vaccine or vaccine component, but the committee considered that the reports could be theoretically supportive of causality for the combination but not in themselves sufficient to allow a firm judgment regarding causality.

## CAUSALITY AND WEIGHT OF EVIDENCE

As discussed in detail in [Chapter 2](#), the committee considered four types of evidence: biologic plausibility; case reports, case series, and uncontrolled observational studies; controlled observational studies; and controlled clinical trials. The committee used qualitative and quantitative approaches to weigh each type of evidence. [Table 1-1](#) contains a summary of the different types of evidence for every vaccine-adverse event relation studied. The committee believes that although it is plausible that there is a causal relation between any of the vaccine-adverse event associations under review, plausibility has been demonstrated only for certain ones of these. Therefore, information on the plausibility of a causal relation was classified in [Table 1-1](#) as either theoretical only or as demonstrated. The other types of evidence were classified in [Table 1-1](#) as nonexistent, indeterminate, or as weighing, on the whole, for or against a determination of a causal relation. The consideration of all four types of evidence as a whole led to a conclusion of the final weight of evidence regarding causality. [Table 1-2](#) contains these conclusions.

**TABLE 1-1**

### Summary of the Evidence For or Against a Determination of a Causal Relation<sup>a</sup>

Vaccine and Adverse Event	Biologic Plausibility <sup>b</sup>	Case Reports, Case Series, and Uncontrolled Observational Studies	Controlled Observational Studies and Controlled Clinical Trials
<i>Diphtheria and Tetanus Toxoids<sup>c</sup></i>			
Encephalopathy	Demonstrated	Indeterminate	Against (DT) No data (Td, T)
Infantile spasms <sup>d</sup> (DT)	Theoretical	No data	Against

only)	cal only			
Residual seizure disorders other than infantile spasms	Theoreti- cal only	Indeterminate (DT, T)	No data	No data
Demyelinating diseases of the central nervous system	Demon- strated	For		No data
Guillain-Barré syndrome	Demon- strated	For (T)	Indeterminate (DT, Td)	No data
Mononeuropathy	Theoreti- cal only	Indeterminate (T, Td)	No data	No data
Brachial neuritis	Theoreti- cal only	For (T)	Indeterminate (Td)	No data

Vaccine and Ad-verse Event	Biologic Plausibili- ty <sup>b</sup>	Case Reports, Case Series, and Un- controlled Observational Studies	Controlled Observational Studies and Controlled Clinical Trials
Arthritis	Theoreti- cal only	Indeterminate	No data
Erythema multiforme	Theoreti- cal only	Indeterminate (DT, Td)	NO data (T)
Anaphylaxis	Demon- strated	For (T)	Indeterminate (DT, Td)
Death from SIDS (DT only) <sup>e</sup>	Theoreti- cal only	Indeterminate	Against
Measles Vaccine <sup>f</sup>			
Encephalopathy	Demon- strated	Indeterminate	Indeterminate
Subacute scleros- ing panencephalitis	Demon- strated	Indeterminate	Indeterminate
Residual seizure disorder	Demon- strated	Indeterminate	No data
Sensorineural deafness	Theoreti- cal only	Indeterminate (MMR)	No data
Optic neuritis	Demon- strated	Indeterminate	No data
Transverse myelitis	Demon- strated	Indeterminate	No data
Guillain-Barré syndrome	Demon- strated	Indeterminate	No data
Thrombocytopenia	Demon- strated	Indeterminate (measles)	For (MMR)
Insulin-dependent diabetes mellitus	Theoreti- cal only	Indeterminate	Indeterminate (measles) No data (MMR)

Vaccine and Adverse Event	Biologic Plausibility <sup>b</sup>	Case Reports, Case Series, and Uncontrolled Observational Studies	Controlled Observational Studies and Controlled Clinical Trials
Anaphylaxis	Theoretical only	For	No data
Death from vaccine-strain vital infection <sup>e</sup>	Demonstrated	For	No data
<i>Mumps Vaccine</i> <sup>f</sup>			
Encephalopathy	Demonstrated	Indeterminate	No data
Aseptic meningitis	Demonstrated	Indeterminate	No data
Residual seizure disorder	Theoretical only	No data	No data
Neuropathy	Theoretical only	No data	No data
Sensorineural deafness	Demonstrated	Indeterminate (MMR)	No data
Insulin-dependent diabetes mellitus	Demonstrated	Indeterminate	Indeterminate
Sterility	Demonstrated	No data	No data
Thrombocytopenia	Demonstrated	Indeterminate	No data
Anaphylaxis	Theoretical only	Indeterminate (MMR)	No data

Vaccine and Adverse Event	Biologic Plausibility <sup>b</sup>	Case Reports, Case Series, and Uncontrolled Observational Studies	Controlled Observational Studies and Controlled Clinical Trials
<i>Polio Vaccine (OPV and IPV)</i> <sup>g</sup>			
Guillain-Barré syndrome	Demonstrated (OPV) Theoretical only (IPV)	For (OPV) Indeterminate (IPV)	For (OPV) No data (IPV)
Transverse myelitis	Demonstrated (OPV) Theoretical only (IPV)	Indeterminate (OPV) No data (IPV)	No data
Poliomyelitis (OPV only)	Demonstrate	For	No data
Thrombocytopenia (IPV)	Theoretical only	No data	No data
Anaphylaxis (IPV)	Theoretical only	No data	No data
Death from SIDS <sup>e</sup>	Theoretical only	Indeterminate	Indeterminate
Death from vaccine-strain vital in-	Demonstrated	For	No data

fection, including from paralytic

polio myelitis (OPV only)<sup>e</sup>

Hepatitis B Vaccine

Guillain-Barré syndrome	Demonstrated	Indeterminate	No data
Demyelinating diseases of the central nervous system	Demonstrated	Indeterminate	No data
Arthritis	Demonstrated	Indeterminate	No data
Anaphylaxis	Theoretical only	For	No data
Death from SIDS <sup>e</sup>	Theoretical only	Indeterminate	No data

Vaccine and Adverse Event	Biologic Plausibility <sup>b</sup>	Case Reports, Case Series, and Uncontrolled Observational Studies	Controlled Observational Studies and Controlled Clinical Trials
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*Haemophilus influenzae* type b Vaccine

Guillain-Barré syndrome	Theoretical only	Indeterminate	No data
Transverse myelitis	Theoretical only	Indeterminate	No data
Thrombocytopenia	Theoretical only	Indeterminate	Indeterminate
Susceptibility to early Hib disease <sup>h</sup>	Demonstrated	Indeterminate	For (PRP) Against (conjugated)
Anaphylaxis	Theoretical only	Indeterminate	No data
Death from SIDS <sup>e</sup>	Theoretical only	Indeterminate	No dam

<sup>a</sup> Indeterminate indicates that there is evidence in this category, but the committee did not consider that, on the whole, it weighed either for or against a causal relation. No data indicates that the committee did not find data of tiffs type directly bearing on a causal relation between the vaccine and the adverse event.

<sup>b</sup> The committee considered all adverse events to be theoretically plausible and, therefore, classified plausibility in support of causality as either theoretical only or demonstrated. Demonstrated biologic plausibility refers to information on the known effects of the natural disease against which the vaccine is given and the results of animal experiments and in vitro studies.

<sup>c</sup> Unless noted otherwise, the classification for tetanus toxoid (T), diphtheria-tetanus toxoid for pediatric use (DT), and tetanus-diphtheria toxoid for adult use (Td) is the same. The committee was not charged with assessing monovalent diphtheria toxoid or the combined diphtheria and tetanus toxoids and pertussis vaccine (DPT). In [Appendix A](#), see the Executive Summary of *Adverse Effects of Pertussis and Rubella Vaccines* for conclusions about DPT.

<sup>d</sup> Infantile spasms occur only in the age group that receives DT but not Td or T. A possible causal relation between infantile spasms and Td and T was not examined.

<sup>e</sup> In this table, the committee summarizes the data regarding the causal relation between the vaccine and only those deaths that are classified as sudden infant death syndrome (SIDS) or that are a consequence of vaccine-strain viral infection. SIDS occurs primarily in infants too young to receive tetanus and diphtheria toxoids for adult use, measles vaccine, mumps vaccine, or usually, tetanus toxoid. Therefore, a relation between these vaccines and SIDS was not assessed. If the evidence favors the acceptance of (or establishes) a causal relation between a vaccine and an adverse event, and if that adverse event can be fatal, then in the committee's judgment the evidence favors the acceptance of (or establishes) a causal relation between the vaccine and death from the adverse event. Direct evidence regarding death in association with a potentially fatal adverse event that itself is causally related to the vaccine is limited to tetanus-diphtheria toxoid for adult use and Guillain-Barré syndrome, tetanus toxoid and anaphylaxis, and oral polio vaccine (OPV) and poliomyelitis. Direct evidence regarding death in association with a potentially fatal adverse event that itself is causally related to the vaccine is lacking for measles vaccine and anaphylaxis, MMR and anaphylaxis, OPV and Guillain-Barré syndrome, hepatitis B vaccine and anaphylaxis, and *Haemophilus influenzae* type b unconjugated PRP vaccine and early-onset *Haemophilus influenzae* type b disease in children age 18 months or older who receive their first Hib immunization with unconjugated PRP vaccine. See [Chapter 10](#) for details. The data are indeterminate regarding the causal relation between the vaccine and causes of death other than those discussed above. Data regarding death as an adverse consequence of the vaccines under review are discussed in [Chapter 10](#) rather than in the vaccine-specific chapters.

<sup>f</sup> The committee was charged with assessing the causal relation between several adverse events and measles vaccine or mumps vaccine. The committee was not charged with assessing monovalent rubella vaccine. In [Appendix A](#), see the Executive Summary of *Adverse Effects of Pertussis and Rubella Vaccines* for conclusions regarding rubella vaccine. (MMR) indicates that the data derive exclusively from the multivalent preparation.

<sup>g</sup> OPV is oral polio vaccine; IPV is inactivated polio vaccine.

<sup>h</sup> The committee assessed data regarding the increased susceptibility to *Haemophilus influenzae* type b disease within 7 days of immunization with *Haemophilus influenzae* type b vaccine. For this adverse event only, the committee was able to separate the data regarding the unconjugated (PRP) vaccine from the data regarding the conjugated vaccines.

TABLE 1-2

## Conclusions Based on the Evidence Bearing on Causality

DT/Td/T	Measles <sup>a</sup>	Mumps <sup>a</sup>	OPV/IPV <sup>b</sup>	Hepatitis B	<i>H. influenzae</i> type <sup>b</sup>
Category, 1: No Evidence Bearing on a Causal Relation					
		Neuropathy	Transverse myelitis (IPV)		
		Residual seizure disorder	Thrombocytopenia (IPV)		
			Anaphylaxis (IPV)		
Category, 2: The Evidence Is Inadequate to Accept or Reject a Causal Relation					
Residual seizure disorder other than infantile spasms	Encephalopathy	Encephalopathy	Transverse myelitis (OPV)	Guillain-Barré syndrome	Guillain-Barré syndrome
	Subacute sclerosing panencephalitis	Aseptic meningitis			
			Guillain-Barré syndrome (IPV)	Demyelinating diseases of the central nervous system	Transverse myelitis



Demyelinating diseases of the central nervous system	Residual seizure	Sensorineural deafness (MMR)	Death from SIDS <sup>c</sup>	Thrombocytopenia Anaphylaxis
Mononeuropathy	Sensorineural deafness (MMR)	Insulin-dependent diabetes mellitus	Arthritis	
Arthritis	Optic neuritis	Sterility	Death from SIDS <sup>c</sup>	Death from SIDS <sup>c</sup>

DT/Td/T	Measles <sup>a</sup>	Mumps <sup>a</sup>	OPV/IPV <sup>b</sup>	He- pati- tis B	H. influenzae type <sup>b</sup>
Erythema multiforme	Transverse myelitis Guillain-Barré syndrome Thrombocytopenia Insulin-dependent diabetes mellitus	Thrombocytopenia Anaphylaxis <sup>d</sup>			
Category 3: The Evidence Favors Rejection of a Causal Relation					
Encephalopathy <sup>e</sup> Infantile spasms (DT only) <sup>f</sup> Death from SIDS (DT only) <sup>f,g</sup>					Early onset H. influenzae <sup>b</sup> disease (conjugate vaccines)
Category 4: The Evidence Favors Acceptance of a Causal Relation					
Guillain-Barré syndrome <sup>h</sup> Brachial neuritis <sup>h</sup>	Anaphylaxis <sup>d</sup>	Guillain-Barré syndrome (OPV)			Early-onset H. influenzae <sup>b</sup> disease in children age 18 months or older who receive their first Hib immunization with unconjugated PRP vaccine

DT/Td/T	Measles <sup>a</sup>	Mumps <sup>a</sup>	OPV/IPV <sup>b</sup>	Hepatitis B	H. influenzae type <sup>b</sup>
Category 5: The Evidence Establishes a Causal Relation					
Anaphylaxis <sup>h</sup>	Thrombocytopenia (MMR)		Poliomyelitis in recipient or contact (OPV)	Anaphylaxis	
	Anaphylaxis (MMR) <sup>d</sup> Death from measles vaccine-strain viral infection <sup>c,i</sup>		Death from polio vaccine-strain viral infection <sup>c,i</sup>		

<sup>a</sup> If the data derive from a monovalent preparation, then in the committee's judgment the causal relation extends to multivalent preparations. If the data derive exclusively from MMR, that is so indicated by (MMR). In the absence of any data on the monovalent preparation, in the committee's judgment the causal relation determined for the multivalent preparations does not extend to the monovalent components.

<sup>b</sup> For some adverse events, the committee was charged with assessing the causal relation between the adverse event and only oral polio vaccine (OPV) (paralytic and nonparalytic poliomyelitis) or only inactivated polio vaccine (IPV) (anaphylaxis and thrombocytopenia). If the conclusions are different for OPV than for IPV for the other adverse events, that is so noted.

<sup>c</sup> This table lists weight-of-evidence determinations only for deaths that are classified as SIDS and deaths that are a consequence of vaccine-strain adverse event can be fatal, then in the committee's judgment the evidence favors the acceptance of (or establishes) a causal relation between the vaccine and death from the adverse event. Direct evidence regarding death in association with a vaccine-associated adverse event is limited to tetanus-diphtheria toxoid for adult use (Td) and Guillain-Barré syndrome, tetanus toxoid and anaphylaxis, and OPV and poliomyelitis. Direct evidence regarding death in association with a potentially fatal adverse event that itself is causally related to the vaccine is lacking for measles vaccine and anaphylaxis, MMR and anaphylaxis, OPV and Guillain-Barré syndrome, hepatitis B vaccine and anaphylaxis, and H. influenzae type b unconjugated PRP vaccine and early-onset H. influenzae type b disease in children age 18 months or older who receive their first Hib immunization with unconjugated PRP vaccine. See [Chapter 10](#) for details.

<sup>d</sup> The evidence that establishes a causal relation for anaphylaxis derives from MMR. The evidence regarding monovalent measles vaccine favors acceptance of a causal relation, but are less convincing, mostly because of incomplete documentation of symptoms or the possible attenuation of symptoms by medical intervention.

<sup>e</sup> The evidence derives from studies of diphtheria-tetanus toxoid for pediatric use (DT). If the evidence favors rejection of a causal relation between DT and encephalopathy, then in the committee's judgment the evidence favors rejection of a causal relation between Td and tetanus toxoid and encephalopathy.

<sup>f</sup> Infantile spasms and SIDS occur only in an age group that receives DT but not Td or tetanus toxoid.

<sup>g</sup> The evidence derives mostly from DPT. Because there are supportive data favoring rejection of a causal relation between DT and SIDS as well, if the evidence favors rejection of a causal relation between DPT and SIDS, then in the committee's judgment the evidence favors rejection of a causal relation between DT and SIDS.

<sup>h</sup> The evidence derives from tetanus toxoid. If the evidence favors acceptance of (or establishes) a causal relation between tetanus toxoid and an adverse event, then in the committee's judgment the evidence favors acceptance of (or establishes) a causal relation between DT and Td and the adverse event as well.

<sup>i</sup> The data come primarily from individuals proven to be immunocompromised.

The committee organized these conclusions into five categories. Because some confusion has arisen over the meaning of the category descriptions used by the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines, despite extensive explanations in both the footnotes and the text, the Vaccine Safety Committee adopted some minor modifications in wording intended to help in the interpretation of the present report. To facilitate reading by those familiar with the report of the previous committee, the present committee maintained both the number of categories (five) and the order of those categories but modified the wording in an attempt to clarify its meaning. However, the Vaccine Safety Committee (which has some overlap in committee membership and staff with the earlier committee) believes that the categories represent the same concepts intended by the predecessor committee. The categories are:

1. No evidence bearing on a causal relation.
2. The evidence is inadequate to accept or reject a causal relation.
3. The evidence favors rejection of a causal relation.
4. The evidence favors acceptance of a causal relation.
5. The evidence establishes a causal relation.

Chapter 2 contains a discussion of the criteria used by the committee for each determination of the final weight of evidence.

The evidence favors rejection of, favors acceptance of, or establishes a causal relation between a vaccine and an adverse event in approximately one-third of the relations studied. For the other relations the evidence was inadequate to accept or reject a causal relation or there was no evidence bearing on the relation. It is important to note that the use of the term *inadequate* does not necessarily imply that the data were scarce. In some cases the committee identified an abundance of data. However, as a whole, it did not favor either acceptance or rejection of a causal relation. In the lists below, the superscript letters refer to the appropriate notes in Table 1-2. The notes in Tables 1-1 and 1-2 are integral to interpretation of the findings. The committee reached the following conclusions regarding causality.

The evidence favors rejection of a causal relation between:

- diphtheria and tetanus toxoids and encephalopathy,<sup>e</sup> infantile spasms,<sup>f</sup> and death from sudden infant death syndrome (SIDS),<sup>f,g</sup> and
- conjugate Hib vaccines and early-onset Hib disease.

- diphtheria and tetanus toxoids and Guillain-Barré syndrome<sup>h</sup> and brachial neuritis,<sup>h</sup>
- measles vaccine and anaphylaxis,<sup>d</sup>
- oral polio vaccine and Guillain-Barré syndrome, and
- unconjugated (PRP) Hib vaccine and early-onset Hib disease in children age 18 months or older who receive their first Hib immunization with unconjugated (PRP) vaccine.

The evidence establishes a causal relation between:

- diphtheria and tetanus toxoids and anaphylaxis,<sup>h</sup>
- measles vaccine and death from measles vaccine-strain viral infection,<sup>c,i</sup>
- measles-mumps-rubella vaccine and thrombocytopenia and anaphylaxis,
- oral polio vaccine and poliomyelitis and death from polio-vaccine-strain viral infection,<sup>c,i</sup> and
- hepatitis B vaccine and anaphylaxis.

For the vast majority of vaccine-adverse event relations studied, the data came predominantly from uncontrolled studies and case reports. Most of the pathologic conditions studied are rare in the general population. The risk of developing these conditions because of vaccination would *seem* to be low. Without age-specific incidence rates and relative risk estimates, however, it is not possible to calculate the proportion of individuals whose condition is causally related to a vaccine. When the data permitted, such calculations (i.e., the risk difference or excess risk) were made and can be found in the conclusions in Chapters 5 through 9. Because age-specific incidence rates were not available for many of the pathologic conditions studied and because controlled epidemiologic studies of these relations are lacking, few such estimates could be made.

## NEED FOR RESEARCH AND SURVEILLANCE

During its attempt to find evidence regarding causality, the committee identified needs for research and surveillance of adverse events. Work in these areas will help to ensure that all vaccines used are as free from the risk of causing adverse events as possible. Some of the needs identified are for increased surveillance of reports of demyelinating disease and arthritis following hepatitis B vaccination, better follow-up of reports of death and other serious adverse events following vaccination, increased use of large databases (currently used only on a small scale) to supplement passive surveillance reporting systems, and disease registries for the rare pathologic conditions studied by the committee.

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# EXHIBIT 290

## Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality (1994)

### **Chapter:** 11 Need for Research and Surveillance

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## **11**

### **Need for Research and Surveillance**

The lack of adequate data regarding many of the adverse events under study was of major concern to the committee. Presentations at public meetings indicated that many parents and physicians share this concern. Although the committee was not charged with proposing specific research investigations, in the course of its reviews additional obvious needs for research and surveillance were identified, and those are briefly described here.

### **DIPHTHERIA AND TETANUS TOXOIDS**

Recent advances in molecular analysis of diphtheria and tetanus toxins make it possible to construct mutant toxins that would be potentially safer, more immunogenic, and more readily purified for use as vaccines. A nontoxic variant of diphtheria toxin (CRM<sub>197</sub>) is already used as a protein carrier molecule in one of the licensed *Haemophilus influenzae* type b polysaccharide-protein conjugate vaccines (see [Chapter 9](#)). If mutant toxin vaccines are more immunogenic than the presently used chemically inactivated toxins, successful immunization might be achieved with fewer doses and fewer adverse events.

The possibility of lot-specific reactions to diphtheria and tetanus toxoids, as has been demonstrated for diphtheria and tetanus toxoids and pertussis vaccine preparations, suggests that studies could be more revealing if the vaccines were tracked by lot.

### **MEASLES AND MUMPS VACCINES**

Understanding the molecular basis for the risk of aseptic meningitis after immunization with the Urabe mumps strain (compared to the experience with the Jeryl Lynn strain) might lead to better understanding of the pathogenetic capacity of mumps virus and to principles of viral pathogenesis that would aid in the development of safe attenuated virus vaccines in the future.

Insulin-dependent diabetes mellitus (IDDM) is a serious and relatively common disorder. The large number of reports raising the suspicion that mumps vaccine might induce the onset of IDDM suggests the need for systematic study of the question.

## **POLIO VACCINES**

There is a need to understand the basis for reversion of oral polio vaccine to a more virulent form to prevent its occurrence.

## **HEPATITIS B VACCINES**

Evidence is inadequate to accept or reject a causal relation between hepatitis B vaccine and Guillain-Barré syndrome, transverse myelitis, optic neuritis, multiple sclerosis, or other demyelinating syndromes. The absence of reports of such outcomes in large-scale field trials suggests that if hepatitis B vaccine causes these adverse events, it does so at a very low frequency. Nevertheless, the number of reports questioning the relation between hepatitis B vaccine to one or the other of these disorders of similar character suggests the need for systematic research.

The possibility that hepatitis B vaccine can cause an exacerbation of rheumatoid arthritis should be carefully evaluated in a population-based study.

## **GUILLAIN BARRÉ SYNDROME**

The committee found that the evidence favors acceptance of a causal relation between tetanus toxoid and Guillain-Barré syndrome (GBS) and between oral polio vaccine and GBS. For the other vaccines, the association with GBS is inconclusive, and research is needed to clarify the association. The following information is potentially obtainable through research: (1) the background incidence of GBS in the U.S. by year of life in the pediatric age group, particularly in infants and preschool-age children; (2) the incidence of GBS after the receipt of each vaccine and combination of vaccines administered to children or adults; and (3) more precise knowledge of the mechanisms and sequence of events that result in vaccine-induced GBS.

## **DEATH**

The committee encourages active and aggressive follow-up of the reports to passive surveillance system of death in association with immunization. This follow-up should be timely and might include elements such as medical records, laboratory tests, and autopsy results. See the section on General Surveillance and Epidemiologic Studies for elaboration.

## **SIMULTANEOUS ADMINISTRATION OF MORE THAN ONE VACCINE**

The committee was able to identify little information pertaining to the risk of serious adverse events following administration of multiple vaccines simultaneously. This is an issue of increasing concern as more vaccines and vaccine combinations are developed for routine use. Both pre- and postmarketing research should address the issue.

## **RISK-MODIFYING FACTORS**

The committee was able to identify little information pertaining to why some individuals react adversely to vaccines when most do not. When it is clear that a vaccine can cause a specific adverse event, research should be encouraged to elucidate the factors that put certain people at risk for that adverse reaction.



## GENERAL SURVEILLANCE AND EPIDEMIOLOGIC STUDIES

Postmarketing surveillance of licensed vaccines in the United States depends upon voluntary reporting. Large numbers of alleged adverse events are reported to the Vaccine Adverse Event Reporting System (VAERS) of the Centers for Disease Control and Prevention and the U.S. Food and Drug Administration. The committee found, however, that follow-up of serious adverse events was often incomplete, and the reported event was often not confirmed because of insufficient clinical, laboratory, or pathologic data. The committee suggests that, in the least, research should be conducted on the performance of passive reporting systems like VAERS. What is the quality and completeness of the information supplied? Can the reports received be used to estimate the true risk of vaccine-induced adverse events? Perhaps most important, how well does the surveillance system detect new adverse events, events not previously reported in the medical literature or demonstrated in epidemiologic studies?

The committee encourages the consideration of a more active system. Such a system might follow a representative sample of new vaccine recipients rather than the population at large. Alternatively, a randomly selected subgroup of serious adverse events reported to VAERS might be investigated fully. This latter approach suffers the inevitable limitations of retrospective review. It may be necessary to retain some broad-based passive reporting system to serve an early-warning function for unpredicted adverse events.

The committee found that a judgment regarding causality was often limited by the absence of background data for the occurrence of the pathologic condition (the putative adverse event) in apparently normal individuals not recently exposed to the vaccine. Regional or national disease registries could be established for those rare but serious conditions suspected of sometimes being caused by one or more licensed vaccines, for example, GBS, transverse myelitis, optic neuritis, and Stevens-Johnson syndrome. Such disease registries, if reasonably complete, would provide information about the descriptive epidemiology of these conditions, including age-, sex-, and race-specific background incidence rates. This information would facilitate the performance of case-control studies and other attempts to investigate vaccines as potential causes of the disorders.

The committee believes that future clinical trials of vaccines licensed or under development should study the serious adverse events examined by the present committee and its predecessor committee. Although any single trial may be too small to detect an effect of vaccine on rare adverse events, meta-analyses of several large trials may provide useful information. Meta-analysis could also be used to improve the statistical power of case-control studies to detect rare sequelae of vaccine administration.

With the existence of the large databases that have recently been established for defined populations, cohort studies become a feasible and desirable epidemiologic method of detecting the adverse effects of vaccines. Cohort studies would also permit the follow-up of patients exposed to specific vaccine types or batches that are suspected (e.g., on the basis of case reports) of being associated with a pathologic condition. Here, too, meta-analyses of cohort studies from different settings and different databases may permit identification of effects not detectable within individual studies.

# EXHIBIT 291

## Adverse Effects of Vaccines: Evidence and Causality (2012)

**Chapter:** Summary

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## Summary

Congress passed the National Childhood Vaccine Injury Act (P.L. 99-660) in 1986. The legislation was intended to bolster vaccine research and development through federal coordination of vaccine efforts in government by providing relief to vaccine manufacturers who reported at the time that financial burdens from awards in the tort system threatened their financial viability. The legislation was also intended to address concerns about the safety of vaccines through a multipronged approach involving instituting a compensation program financed by an excise tax on covered vaccines, setting up a passive surveillance system for vaccine adverse events, and providing information to consumers.

Sections 312 and 313 of the legislation required the secretary of the U.S. Department of Health and Human Services to consult with the Institute of Medicine (IOM) to conduct a review of the scientific literature related to a set of serious adverse events<sup>1</sup> following immunizations recommended for use in children. Two reports were issued (IOM, 1991, 1994). These reports contain a framework for causality assessment of adverse events following vaccination. The reports embraced all vaccines covered by the National Vaccine Injury Compensation Program (VICP) up to that point: diphtheria- and tetanus-toxoids and whole cell pertussis (DTwP) vaccine<sup>2</sup> and other tetanus toxoid-containing vaccines; measles, mumps, and rubella

<sup>1</sup> Adverse events are distinguished from adverse effects in that an event is something that occurs but may not be causally associated, whereas an adverse effect implies causation. All adverse effects are adverse events, but not all adverse events are adverse effects.

<sup>2</sup> Acellular pertussis vaccine (aP) has replaced whole cell pertussis vaccine in the United States.

(MMR) vaccines; *Haemophilus influenzae* type B vaccine; hepatitis B vaccine; and both inactivated and oral polio vaccines.<sup>3</sup> The reports informed the secretary's review of the Vaccine Injury Table. The reports have also been referenced extensively as a source of definitive scientific understanding of the evidence by Special Masters in decisions regarding injuries not listed on the Vaccine Injury Table.

The IOM was subsequently asked to review specific vaccine safety concerns in a series of reports requested by the Centers for Disease Control and Prevention (CDC). These reports (IOM, 2001a,b, 2002a,b, 2003a,b,

2004a,b) included causality assessments similar to the previous IOM reports, but included other conclusions and recommendations regarding research, communications, and policy review.

## CHARGE TO THE COMMITTEE

In 2009 the IOM entered into a contract with the Health Resources and Services Administration (HRSA)<sup>4</sup> to convene a committee of experts to review the epidemiologic, clinical, and biological evidence regarding adverse health events associated with specific vaccines covered by the VICP. The committee was composed of individuals with expertise in pediatrics, internal medicine, neurology, immunology, immunotoxicology, neurobiology, rheumatology, epidemiology, biostatistics, and law.

The vaccines to be reviewed included varicella zoster vaccine; influenza vaccines;<sup>5</sup> hepatitis B vaccine; human papillomavirus vaccine (HPV); tetanus toxoid-containing vaccines other than those containing the whole cell pertussis component; measles, mumps, and rubella vaccines; hepatitis A vaccine; and meningococcal vaccines. It is expected that the report will provide the scientific basis for review and adjudication of claims of vaccine injury by the VICP.

HRSA presented a list of specific adverse events for the committee to review (see Table S-1). The selection criteria was described at the first committee meeting (Johann-Liang, 2009) as including the vast majority of adverse events in the claims for compensation. The committee added adverse events to the list if it identified epidemiologic studies or case reports for an adverse event not originally assigned by HRSA. These additions were all-cause mortality and seizures following influenza vaccine; optic neuritis

<sup>3</sup> Vaccines are included in the VICP if they are recommended by the CDC for routine administration in children and are subject to an excise tax. Adults who experience an adverse reaction to one of these “childhood” vaccines are also covered by the program.

<sup>4</sup> The CDC and the National Vaccine Program Office also provided funds for the project via the contract with HRSA.

<sup>5</sup> The 2009 H1N1 influenza vaccine is covered by the Countermeasures Injury Compensation Program, and evidence about its safety is not covered in this report.

**TABLE S-1 Adverse Events and Causality Conclusions Included in the Vaccine Chapters**

Adverse event	MMR Vaccine Chapter 4	Varicella Vaccine Chapter 5	Influenza Vaccine Chapter 6	Hepatitis A Vaccine Chapter 7	Hepatitis B Vaccine Chapter 8	HPV Vaccine Chapter 9	DT-, TT-, and aP- Containing Vaccines Chapter 10	Meningococcal Vaccine Chapter 11	Injection- Related Events Chapter 12
Disseminated Oka VZV without Other Organ Involvement		CS							
Disseminated Oka VZV with Subsequent Infection Resulting in Pneumonia, Meningitis, or Hepatitis		CS <sup>a</sup>							
Vaccine Strain Viral Reactivation without Other Organ Involvement		CS							
Vaccine Strain Viral Reactivation with Subsequent Infection Resulting in Meningitis or Encephalitis		CS							
Measles Inclusion Body Encephalitis	CS <sup>a,b</sup>								
Encephalitis	I		I		I		I	I	
Encephalopathy	I	i	I		I		I	I	
Infantile Spasms							I		

Varicella      Influenza      Hepatitis A      Hepatitis B      DT-, TT-,  
and aP-  
Containing      Injection-  
Meningococcal Related

Adverse event	MMR Vaccine Chapter 4	MMR Vaccine Chapter 5	MMR Vaccine Chapter 6	Vaccine Chapter 7	Vaccine Chapter 8	HPV Vaccine Chapter 9	MMR Vaccine Chapter 10	Vaccine Chapter 11	Events Chapter 12
Febrile Seizures	CS								
Afebrile Seizures	I								
Seizures		I	I <sup>c</sup>		I		I		
Meningitis	I <sup>c</sup>								
Cerebellar Ataxia		I							
Ataxia	I						I		
Autism	FR						I		
Acute Disseminated Encephalomyelitis	I	I	I	I	I	I	I	I	
Transverse Myelitis	I	I	I	I	I	I	I	I	
Optic Neuritis	I <sup>c</sup>		I <sup>c</sup>		I <sup>c</sup>		I <sup>c</sup>		
Neuromyelitis Optica	I <sup>c</sup>		I		I	I			
Multiple Sclerosis Onset in Adults	I		I		I		I		
Multiple Sclerosis Onset in Children	I				I				
Multiple Sclerosis Relapse in Adults			I		I		I		
Multiple Sclerosis Relapse in Children					I		I		
Multiple Sclerosis				I		I		I	
First Demyelinating Event in Adults					I				
First Demyelinating Event in Children					I				
Guillain-Barré Syndrome	I	I	I	I	I	I	I	I	
Chronic Inflammatory Disseminated Polyneuropathy	I		I	I	I	I	I	I	
Opsoclonus Myoclonus Syndrome	I						I		
Bell's Palsy			FR	I			I		
Brachial Neuritis	I		I		I	I			
Amyotrophic Lateral Sclerosis						I			
Small Fiber Neuropathy		I <sup>c</sup>	I						
Anaphylaxis	CS	CS	CS	I	CS <sup>d</sup>	FA	CS <sup>e</sup>	CS	
Chronic Urticaria							I		
Scrum Sickness							I		

Adverse event	MMR Vaccine Chapter 4	Varicella Vaccine Chapter 5	Influenza Vaccine Chapter 6	Hepatitis A Vaccine Chapter 7	Hepatitis B Vaccine Chapter 8	HPV Vaccine Chapter 9	DT-, TT-, and aP- Containing Vaccines Chapter 10	Meningococcal Vaccine Chapter 11	Injection- Related Events Chapter 12
Inactivated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children and Adults			FR						
Live Attenuated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children Younger Than 5 Years of Age			I						
Live Attenuated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Persons 5 Years of Age or Older			I						
Erythema Nodosum					I <sup>c</sup>				

Systemic Lupus

Erythematosis

Vasculitis

Polyarteritis Nodosa

I

I

I

I

Psoriatic Arthritis

I

Reactive Arthritis

I

Rheumatoid Arthritis

I

Juvenile Idiopathic Arthritis

I

Transient Arthralgia in Women

FA<sup>f</sup>

Transient Arthralgia in Children

FA

Transient Arthralgia

I

Chronic Arthralgia in Women

I

Chronic Arthritis in Women

I

Chronic Arthropathy in Children

I

Arthropathy in Men

I

Arthropathy

I

I

I

Type 1 Diabetes

FR

FR

Autoimmune Hepatitis

I

Myocarditis

I

Pancreatitis

I

Adverse event	MMR Vaccine Chapter 4	Varicella Vaccine Chapter 5	Influenza Vaccine Chapter 6	Hepatitis A Vaccine Chapter 7	Hepatitis B Vaccine Chapter 8	HPV Vaccine Chapter 9	DT-, TT-, and aP- Containing Vaccines Chapter 10	Meningococcal Vaccine Chapter 11	Injection- Related Events Chapter 12
Hepatitis	I								
Thromboembolic Events							I		
Stroke		I <sup>c</sup>		I					
Hypercoagulable States							I		
Myocardial Infarction				I					
Chronic Fatigue Syndrome	I								
Chronic Headache							I		
Fibromyalgia	I			I		I	I		
Sudden Infant Death Syndrome							I		
Hearing Loss	I								
All Cause Mortality				I <sup>c</sup>					
Oculorespiratory Syndrome				FA <sup>g</sup>					
Thrombocytopenia		I							
Immune Thrombocytopenic Purpura							I		
Complex Regional Pain Syndrome								I	
Deltoid Bursitis									CS
Syncope									CS

NOTE: CS = convincingly supports a causal relationship; FA = favors acceptance of a causal relationship; FR = favors rejection of a causal relationship; I = inadequate to accept or reject a causal relationship.

<sup>a</sup> The committee attributes causation to individuals with demonstrated immunodeficiencies.

<sup>b</sup> The committee attributes causation to the measles component of the vaccine.

<sup>c</sup> Although not originally charged to the committee by the sponsor, the committee considered this adverse event in its review of the literature.

<sup>d</sup> The committee attributes causation to yeast-sensitive individuals.

<sup>e</sup> The committee attributes causation to the tetanus toxoid vaccine. The evidence is inadequate to accept or reject a causal relationship between anaphylaxis and diphtheria toxoid or acellular pertussis vaccine.

<sup>f</sup> The committee attributes causation to the rubella component of the vaccine.

following MMR, influenza, hepatitis B, and DTaP vaccines; neuromyelitis optica and meningitis following MMR vaccine; erythema nodosum following hepatitis B vaccine; and stroke and small fiber neuropathy following varicella vaccine.

It is important to note that the committee was *not* tasked with assessing the benefits (effectiveness) of vaccines or any policy issues related to vaccination. The committee's task is focused only on an assessment of the risk of vaccines.

## ASSESSING THE WEIGHT OF EVIDENCE

Two streams of evidence support the committee's causality conclusions: epidemiologic evidence derived from studies of populations (most often based on observational designs but randomized trials when available), and mechanistic evidence derived primarily from biological and clinical studies in animals and individual humans (see [Figure S-1](#)). Some studies provide evidence capable of addressing both epidemiologic and mechanistic questions. Drawing from both sources of evidence to support causal inference is well established in the literature.

The committee made three assessments for each relationship reviewed. The first assessment applies to the weight of evidence from the epidemiologic literature; the second applies to the weight of evidence from the mechanistic literature. Each individual article (or findings within an article if more than one outcome or vaccine was studied) was evaluated for its strengths and weaknesses. The committee then synthesized the body of evidence of each type (epidemiologic or mechanistic) and assigned a "weight-of-evidence" for each. These weights-of-evidence represent the committee's assessment of the quality and quantity of evidence. The two weight-of-evidence assessments contributed to the third assessment, a conclusion about the causal relationship.

### Weight of Epidemiologic Evidence

Each peer-reviewed epidemiologic study was evaluated for its methodologic limitations (e.g., flawed measurement of either vaccine administration or adverse event, or failure to adequately control confounding variables) and for the precision of the reported results (e.g., the width of the 95% confidence interval around an effect estimate, reflecting the statistical power to detect a significantly increased risk of an adverse event). A specific study involving multiple outcomes or vaccines could have fewer limitations for the analysis of some vaccines or some outcomes than for others. Small clinical studies can be well conducted but the low number of subjects may limit the ability to detect most adverse events. Although most efficacy studies



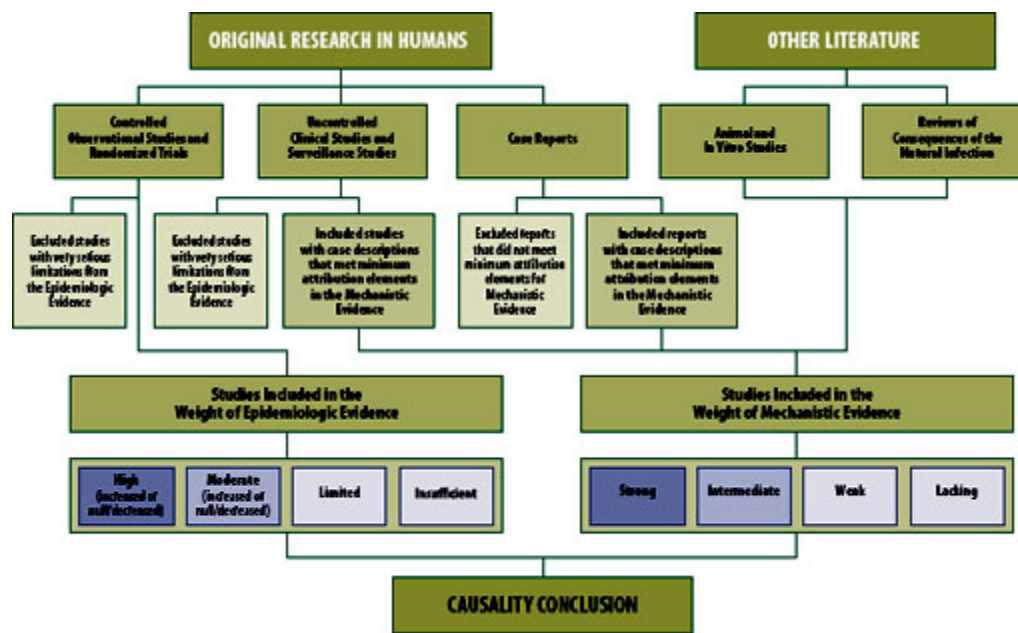


FIGURE S-1 Epidemiologic and mechanistic evidence reviewed by the committee.

include a safety component, the results are often nonspecific (e.g., “no serious adverse events were detected”). The committee was rigorous in assessing the strengths and weaknesses of each epidemiologic study. Some studies reviewed are likely the most reasonably methodologically sound given the nature of the exposure and the outcomes, even if the studies have some residual limitation due to the challenges that often attend such research. Summary paragraphs describe the epidemiologic evidence (as well as the mechanistic evidence and in some circumstances the causality conclusion) more fully than can be captured with the formal and consistent wording of the assessments used in this report.

The committee used a summary classification scheme that incorporates both the quality and quantity of the individual epidemiologic studies and the consistency of the group of studies in terms of direction of effect (i.e., whether the vaccine increases risk, decreases risk, or has no effect on risk). Integral to the assessment is the confidence the committee has that the true effect lies close to the average overall effect estimate for the body of evidence (i.e., collection of reports) reviewed (Schunemann et al., 2011).

The four weight-of-evidence assessments for the epidemiologic evidence are

- High: Two or more studies with negligible methodological limitations that are consistent in terms of the direction of the effect, and taken together provide high confidence.
- Moderate: One study with negligible methodological limitations, or a collection of studies generally consistent in terms of the direction of the effect, that provides moderate confidence.
- Limited: One study or a collection of studies lacking precision or consistency that provides limited, or low, confidence.
- Insufficient: No epidemiologic studies of sufficient quality.

Assessments of high and moderate include a direction of effect. These are to indicate increased risk of the adverse event, decreased risk of the adverse event, or no change in risk of the adverse event or “null.” Assessments of limited or insufficient include no direction of effect.

#### Weight of Mechanistic Evidence

The committee assessed the mechanisms by which the vaccine could cause a specific adverse event by identifying and evaluating clinical and biological evidence. First, the committee searched for evidence in the peer-reviewed literature that a vaccine was or may be a cause of an adverse event in one or more persons (from case reports or clinical studies) in a reasonable time period after the vaccination. Then the committee looked

for other information from the clinical and biological (human, animal, or in vitro studies) literature that would provide evidence of a pathophysiological process or mechanism that is reasonably likely to cause the adverse event or to occur in response to a specific immunization. Chapter 3 contains a discussion of the major mechanisms the committee invokes as possible explanations of how a given adverse event can occur after vaccination.

The committee identified many case reports in the literature describing adverse events following vaccination. For the purposes of this report, *case report* refers to a description of an individual patient; one publication could describe multiple case reports. The committee evaluated each case report using a well-established set of criteria called *attribution elements* for case evaluation (Miller et al., 2000). At a minimum, for a case to factor into the weight-of-evidence assessment, it had to include specific mention of the vaccine administered, evidence of a clinician-diagnosed health outcome, and a specified and reasonable time interval (i.e., temporality or latency) between vaccination and symptoms. Case descriptions that did not have the three basic elements described above were not considered in the mechanistic weight-of-evidence assessments. These three criteria were only necessary but not sufficient to affect the weight of mechanistic evidence. After identifying cases with the three basic elements, the committee looked for evidence in the case descriptions and in other clinical or biological literature of a possible operative mechanism(s) that would support a judgment that the vaccination was related to the adverse event. See Chapter 3 for a description of possible mechanisms identified by the committee.

An important attribute in the evaluation of the clinical evidence from case reports is *rechallenge*, an adverse event that occurred after more than one administration of a particular vaccine in the same individual. Each challenge in a patient, however, must meet the same attributes of reasonable latency, documentation of vaccination receipt, and clinician diagnosis of the health outcome. The value of any case report is much greater if the clinical workup eliminated well-accepted alternative explanations for the condition, thus increasing the possibility that the vaccine could be associated with the adverse event. A particularly strong piece of evidence in the case description is laboratory-confirmed isolation of a vaccine strain virus in the patient.

The committee follows the convention of previous IOM committees in considering the effects of the natural infection as one type, albeit minor, of clinical or biological evidence in support of mechanisms.<sup>6</sup> Other evidence,

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<sup>6</sup> The committee relied on standard textbooks of infectious disease or internal medicine for this evaluation; the committee did not review original research to come to this determination. This is consistent with previous IOM committees tasked with reviewing evidence of causality for vaccine safety. Evidence consisting only of parallels with the natural infections is never sufficient to merit a conclusion other than the evidence is inadequate to accept or reject a causal relationship.

described above, provided much stronger evidence in support of the mechanistic assessment. Evidence from animal studies is also informative if the model of the disease (adverse outcome) is well established as applicable to humans, or if the basic immunology of the vaccine reaction is well understood. In vitro studies can also be informative, but such data were eyed with skepticism regarding their relationship to the human experience.

The committee developed categories for the mechanistic weight-of-evidence assessment. Each assessment includes consideration of the clinical information from case reports and consideration of clinical and

experimental evidence from other sources. The four weight-of-evidence assessments for the mechanistic evidence are

- Strong: One or more cases in the literature, for which the committee concludes the vaccine *was* a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine.
- Intermediate: At least two cases, taken together, for which the committee concludes the vaccine *may be* a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine. On occasion, the committee reviewed evidence consisting of at least two cases that, taken together, while *suggestive*, are nonetheless insufficient to conclude that the vaccine may be a contributing cause of the adverse event. This evidence has been categorized as “low-intermediate.”
- Weak: Insufficient evidence from cases in the literature for the committee to conclude the vaccine may be a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine.
- Lacking: No clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine, regardless of the presence of individual cases in the literature.

### CAUSALITY ASSESSMENT

The committee adopted the approach to causation developed by previous IOM committees. Implicit in these categories is that “the absence of evidence is not evidence of absence.” That is, the committee began its assessment from the position of neutrality; until all evidence was reviewed, it presumed neither causation nor lack of causation. The committee then

moved from that position only when the combination of epidemiologic evidence and mechanistic evidence suggested a more definitive assessment regarding causation, either that vaccines might or might not pose an increased risk of an adverse effect. The categories of causation used by the committee are the following:

- *Evidence convincingly supports<sup>7</sup> a causal relationship*—This applies to relationships in which the causal link is convincing, as with the oral polio vaccine and vaccine-associated paralytic polio.
- *Evidence favors acceptance of a causal relationship*—Evidence is strong and generally suggestive, although not firm enough to be described as convincing or established.
- *Evidence is inadequate to accept or reject a causal relationship*—The evidence is not reasonably convincing either in support of or against causality; evidence that is sparse, conflicting, of weak quality, or merely suggestive—whether toward or away from causality—falls into this category. Where there is no evidence meeting the standards described above, the committee also uses this causal conclusion.
- *Evidence favors rejection of a causal relationship*—The evidence is strong and generally convincing, and suggests there is no causal relationship.

The category of “establishes or convincingly supports no causal relationship” is not used because it is virtually impossible to prove the absence of a relationship with the same certainty that is possible in establishing the presence of one. Even in the presence of a convincing protective effect of a vaccine based on epidemiology, studies may not rule out the possibility that the reaction is caused by vaccine in a subset of individuals. Thus, the framework for this and previous IOM reports on vaccine safety is asymmetrical. The committee began not by assuming the causal relationship does not exist, but by requiring evidence to shift away

from the neutral position that the evidence is “inadequate to accept or reject” a causal relationship.

The committee established a general framework by which the two streams of evidence (epidemiologic and mechanistic) influence the final causality conclusion (see Figure S-2). This framework needed to accommodate the reality that—for any given adverse event relationship reviewed—one or both of the types of evidence could be lacking, the two types of evidence could conflict, or neither type of evidence might definitively influence the causality conclusion. The framework does not accommodate any information regarding the benefit of the vaccine to either population or individual

<sup>7</sup> Previous IOM committees used the term “establishes” instead of “convincingly supports.”

EPIDEMIOLOGIC ASSESSMENT						MECHANISTIC ASSESSMENT					CAUSALITY CONCLUSION			
High (Increased risk)	High (Decreased risk or no effect)	Moderate (Increased risk)	Moderate (Decreased risk or no effect)	Limited	Inadequate	Strong	Intermediate	Low-Intermediate	Weak	Lacking	Inadequate to Accept or Reject	Favors Rejection	Favors Acceptance	Convincingly Supports
High (Increased risk)														Convincingly Supports
						Strong								Convincingly Supports
		Moderate (Increased risk)												Favors Acceptance
							Intermediate							Favors Acceptance
	High (Decreased risk or no effect) <sup>**</sup>													Favors Rejection
			Moderate (Increased risk or no effect), Limited, or Inadequate <sup>***</sup>											Inadequate to Accept or Reject
								Low-Intermediate, Weak, or Lacking <sup>***</sup>						Inadequate to Accept or Reject

<sup>\*\*</sup> Causality concluded to favor rejection only if mechanistic assessment is not strong or intermediate.  
<sup>\*\*</sup> Causality concluded inadequate to accept or reject only if mechanistic assessment is not strong or intermediate.  
<sup>\*\*\*</sup> Causality concluded inadequate to accept or reject only if epidemiologic assessment is not high (increased risk), high (decreased risk or no effect), or moderate (increased risk).

FIGURE S-2 Strength of evidence that determined the causality conclusions.

health. The focus of this particular committee is only on the question of what particular vaccines can cause particular adverse effects.

The framework also had to accommodate known strengths and limitations of both types of evidence. Mechanistic evidence can only support causation, but epidemiologic evidence can support a causal association or can support the absence of (“rejection of”) a causal association in the general population. Mechanistic evidence, particularly that emerging from case reports, occasionally provides compelling evidence of an association between exposure to a vaccine and an adverse event in the individual being studied, but it provides no meaningful information about the risk to the population. Epidemiologic analyses are usually unable to detect an increased or decreased risk that is small, unless the study population is very large or the between-group (e.g., vaccinated vs. unvaccinated) difference in risk is very high (e.g., smoking increases the risk of lung cancer by at least 10-fold). Epidemiologic analyses also cannot identify with certainty which individual in a population at risk will develop the condition.

The committee does not consider a single epidemiologic study—regardless of how well it is designed, the size of the estimated effect, or the narrowness of the confidence interval—sufficient to merit a weight of “high” or, in the absence of strong or intermediate mechanistic evidence, sufficient evidence to support a causality conclusion other than “inadequate to accept or reject a causal relationship.” This requirement

might seem overly rigorous to some readers. However, the Agency for Healthcare Research and Quality advises the Evidence-based Practice Centers that it has funded to produce evidence reports on important issues in health care to view an evidence base of a single study with caution (Owens et al., 2010). It does so due to the inability to judge consistency of results, an important contributor to a strength of evidence, because one cannot “be certain that a single trial, no matter how large or well designed, presents the definitive picture of any particular clinical benefit or harm for a given treatment” (Owens et al., 2010). It is acknowledged by the committee and others (Owens et al., 2010) that policy makers must often make decisions based on only one study. However, the committee is not recommending policy, rather evaluating the evidence using a transparent and justifiable framework.

## CAUSALITY CONCLUSIONS

### Convincingly Supports

The framework allows for a causality conclusion of “convincingly supports” based on an epidemiologic weight-of-evidence assessment of high in the direction of increased risk (which requires at least two well-conducted epidemiologic studies). Strong mechanistic evidence, which requires at least

one case report in which compelling evidence exists that the vaccine indeed did cause the adverse event, always carries sufficient weight for the committee to conclude the evidence convincingly supports a causal relationship. The committee considered the detection of laboratory-confirmed, vaccine-strain virus compelling evidence to attribute the disease to the vaccine-strain virus and not other etiologies. This conclusion can be reached even if the epidemiologic evidence is rated high in the direction of no increased risk or even decreased risk.

The simplest explanation in this circumstance is that the adverse effect is real but also very rare. Stating this another way, if the vaccine *did* cause the adverse effect in one person, then it *can* cause the adverse effect in someone else; however, the isolated report of one convincing case provides no information about the risk of the adverse effect in the total population of vaccinated individuals compared with unvaccinated individuals.

The committee concluded the evidence convincingly supports 14 specific vaccine–adverse event relationships. In all but one of these relationships, the conclusion was based on strong mechanistic evidence with the epidemiologic evidence rated as either limited confidence or insufficient. The convincing evidence regarding varicella vaccine and disseminated Oka varicella zoster virus (VZV) and Oka VZV viral reactivation depended on identification of vaccine-strain virus as documented by polymerase chain reaction, as was the evidence regarding MMR vaccine and measles inclusion body encephalitis. Epidemiologic evidence, as well as mechanistic evidence, convincingly supported the causal relationship between MMR vaccine and febrile seizures. Clinical evidence from case reports and a well-identified mechanism of hypersensitivity reactions convincingly supported the conclusions regarding anaphylaxis and six vaccines (MMR, varicella, influenza, hepatitis B, meningococcal, and tetanus toxoid vaccine). Mechanistic evidence provided the convincing support for the conclusion that injection of vaccine, independent of the antigen involved, can lead to two adverse events: syncope and deltoid bursitis (see [Table S-2](#)).

### Favors Acceptance

A conclusion of “favors acceptance of a causal relationship” must be supported by either epidemiologic evidence of moderate certainty of an increased risk or by mechanistic evidence of intermediate weight. The committee concluded the evidence favors acceptance of four specific vaccine–adverse event relationships. These include HPV vaccine and anaphylaxis, MMR vaccine and transient arthralgia in female adults, MMR vaccine and transient arthralgia in children, and certain trivalent influenza vaccines used in Canada and a mild and temporary oculorespiratory syndrome. The conclusion regarding anaphylaxis was supported by



only mechanistic evidence.

**TABLE S-2** Summary of Causality Conclusions<sup>a</sup>

Chapter	Vaccine	Adverse Event	Epidemiologic Assessment	Studies Contributing to the Epidemiologic Assessment	Mechanistic Assessment	Cases Contributing to the Mechanistic Assessment	Causality Conclusion
S	Varicella	Disseminated Oka VZV without Other Organ Involvement	Insufficient	None	Strong	— <sup>b</sup>	Convincingly Supports
5	Varicella	Disseminated Oka VZV with Subsequent Infection Resulting in Pneumonia, Meningitis, or Hepatitis	Limited (subsequent infection resulting in pneumonia) Insufficient (subsequent infection resulting in meningitis or hepatitis)	1	Strong (in individuals with demonstrated immunodeficiencies)	9	Convincingly Supports <sup>c</sup>
S	Varicella	Vaccine Strain Viral Reactivation without Other Organ Involvement	Insufficient	None	Strong	— <sup>b</sup>	Convincingly Supports
5	Varicella	Vaccine Strain Viral Reactivation with Subsequent Infection Resulting in Meningitis or Encephalitis	Limited (subsequent infection resulting in encephalitis) Insufficient (subsequent infection resulting in meningitis)	1	Strong	6	Convincingly Supports
Chapter	Vaccine	Adverse Event	Epidemiologic Assessment	Studies Contributing to the Epidemiologic Assessment	Mechanistic Assessment	Cases Contributing to the Mechanistic Assessment	Causality Conclusion
4	MMR	Measles Inclusion Body Encephalitis	Insufficient	None	Strong (measles; in individuals with demonstrated immunodeficiencies) Lacking (mumps or rubella)	1 None	Convincingly Supports <sup>c,d</sup>
4	MMR	Febrile Seizures	High (increase)	7	Intermediate	12	Convincingly Supports
4	MMR	Anaphylaxis	Insufficient	None	Strong	43 <sup>e</sup>	Convincingly Supports
5	Varicella	Anaphylaxis	Limited	1	Strong	76 <sup>f</sup>	Convincingly Supports
6	Influenza	Anaphylaxis	Limited	1	Strong	22	Convincingly Supports
8	Heparins B	Anaphylaxis	Insufficient	None	Strong (in yeast-sensitive individuals)	10	Convincingly Supports <sup>g</sup>
10	Tetanus Toxoid	Anaphylaxis	Insufficient	None	Strong	6	Convincingly Supports
11	Meningococcal	Anaphylaxis	Insufficient	None	Strong	1	Convincingly Supports
12	Injection-Related Event	Deltoid Bursitis	Limited	1	Strong	16	Convincingly Supports
12	Injection-Related Event	Syncope	Insufficient	None	Strong	35 <sup>b</sup>	Convincingly Supports
9	HPV	Anaphylaxis	Insufficient	None	Intermediate	36	Favors Acceptance
4	MMR	Transient Arthralgia in Women	Moderate (increase) (rubella) Insufficient (measles or mumps)	4 None	Intermediate (rubella) Lacking	13 None	Favors Acceptance <sup>i</sup>

4	MMR	Transient Arthralgia in Children	Moderate (increase)	7	Weak (rubella) Lacking (measles or mumps)	None	None	Favors Acceptance
6	Influenza	Oculorespiratory Syndrome	Moderate (increase)	3	Intermediate	— <sup>j</sup>		Favors Acceptance <sup>k</sup>
4	MMR	Autism	High (null)	4	Lacking	None		Favors Rejection
6	Influenza	Inactivated Influenza Vaccine and Bell's palsy	High (null)	2	Lacking	None		Favors Rejection

Chapter	Vaccine	Adverse Event	Epidemiologic Assessment	Studies Contributing to the Epidemiologic Assessment	Mechanistic Assessment	Cases Contributing to the Mechanistic Assessment	Causality Conclusion
6	Influenza	Inactivated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children and Adults	High (null)	9	Weak	6	Favors Rejection
4	MMR	Type 1 Diabetes	High (null)	5	Lacking	None	Favors Rejection
10	DT, TT, or aP containing	Type 1 Diabetes	High (null)	5	Lacking	None	Favors Rejection

<sup>a</sup> All other causality conclusions are the evidence is inadequate to accept or reject a causal relationship.

<sup>b</sup> Due to the use of the same surveillance systems in some publications it is likely that some of the cases were presented more than once; thus, it is difficult to determine the number of unique cases.

<sup>c</sup> The committee attributes causation to individuals with demonstrated immunodeficiencies.

<sup>d</sup> The committee attributes causation to the measles component of the vaccine.

<sup>e</sup> Some cases were from passive surveillance systems; however, it is not possible to know how many represent unique cases or were reported elsewhere.

<sup>f</sup> In addition, at least 30 cases were reported to passive surveillance systems; however, it is not possible to know how many represent unique cases or were reported elsewhere.

<sup>g</sup> The committee attributes causation to yeast-sensitive individuals.

<sup>h</sup> In addition, hundreds of cases have been reported to passive surveillance systems; however, it is not possible to know how many represent unique cases or were reported elsewhere.

<sup>i</sup> The committee attributes causation to the rubella component of the vaccine.

<sup>j</sup> Due to the use of the same sample population in some studies it is likely that some of the cases were presented in more than one publication; thus, it is difficult to determine the number of unique cases.

<sup>k</sup> The committee attributes causation to two particular vaccines used in three particular years in Canada.

The other conclusions were supported by both epidemiologic evidence and by mechanistic evidence (see Table S-2).

### Favors Rejection

The framework allows the committee to “favor rejection” of a causal relationship only in the face of epidemiologic evidence rated as high or moderate in the direction of no effect (the null) or of decreased risk and in the absence of strong or intermediate mechanistic evidence in support of a causal relationship. The committee concluded the evidence favors rejection of five vaccine–adverse event relationships. These include MMR vaccine and type 1 diabetes, diphtheria, tetanus, and pertussis (DTaP) vaccine and type 1 diabetes, MMR vaccine and autism, inactivated influenza vaccine and asthma exacerbation or reactive airway disease episodes, and inactivated influenza vaccine and Bell's palsy. The evidence base for these conclusions consisted of epidemiologic studies reporting no increased risk; this evidence was not countered by mechanistic evidence (see Table S-2).



The committee identified two main pathways by which it concludes that the evidence is “inadequate to accept or reject” a causal relationship. The most common pathway to this conclusion occurs when the epidemiologic evidence was of limited certainty or insufficient and the mechanistic evidence was weak or lacking. Another pathway occurs when the epidemiologic evidence is of moderate certainty of no effect but the mechanistic evidence is intermediate in support of an association. The committee analyzed these sets of apparently contradictory evidence and ultimately depended upon their expert judgment in deciding if a conclusion to favor acceptance based on the intermediate mechanistic data was warranted, or if the conclusion remained as “inadequate to accept or reject” a causal relationship.

The vast majority of causality conclusions in the report are that the evidence was inadequate to accept or reject a causal relationship. Some might interpret that to mean either of the following statements:

- Because the committee did not find convincing evidence that the vaccine *does* cause the adverse event, the vaccine is safe.
- Because the committee did not find convincing evidence that the vaccine *does not* cause the adverse event, the vaccine is unsafe.

*Neither of these interpretations is correct.* “Inadequate to accept or reject” means just that—inadequate. If there is evidence in either direction that is suggestive but not sufficiently strong about the causal relationship, it

will be reflected in the weight-of-evidence assessments of the epidemiologic or the mechanistic data. However suggestive those assessments might be, in the end the committee concluded that the evidence was inadequate to accept or reject a causal association.

A list of all conclusions, including the weights of evidence for both the epidemiologic evidence and the mechanistic evidence, can be found in [Appendix D](#).

## SUSCEPTIBILITY

The literature supporting several of the causality conclusions discussed in the previous section indicates that individuals with certain characteristics are more likely to suffer adverse effects from particular immunizations. Individuals with an acquired or genetic immunodeficiency are clearly recognized as at increased risk for specific adverse reactions to live viral vaccines such as MMR and varicella vaccine. Age is also a risk factor; seizures after immunization, for example, are more likely to occur in young children. Thus, the committee was able at times to reach more limited conclusions that did not generalize to the entire population.

## CONCLUDING COMMENT

Committee members spent an enormous amount of time reading thousands of articles. The committee makes 158 causality conclusions in this report. It tried to apply consistent standards when reviewing individual articles and when assessing the bodies of evidence. Some of the conclusions were easy to reach; the evidence was clear and consistent or, in the extreme, completely absent. Some conclusions required substantial discussion and debate. Inevitably, there are elements of expert clinical and scientific judgment involved.

The committee used the best evidence available at the time. The committee hopes that the report is sufficiently transparent such that when new information emerges from either the clinic or the laboratory, others will be able to assess the importance of that new information within the approach and set of conclusions presented in this report.

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# **EXHIBIT 292**



Vaccine Adverse Event Reporting System  
www.vaers.hhs.gov

(index.html)

## VAERS Home (index.html)

VAERS (index.html)

Home (index.html) / About Us

## About VAERS

### Background and Public Health Importance

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Established in 1990, the Vaccine Adverse Event Reporting System (VAERS) is a national early warning system to detect possible safety problems in U.S.-licensed vaccines. VAERS is co-managed by the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA). VAERS accepts and analyzes reports of adverse events (possible side effects) after a person has received a vaccination. Anyone can

report an adverse event to VAERS. Healthcare professionals are required to report certain adverse events and vaccine manufacturers are required to report all adverse events that come to their attention.



VAERS is a passive reporting system, meaning it relies on individuals to send in reports of their experiences to CDC and FDA. VAERS is not designed to determine if a vaccine caused a health problem, but is especially useful for detecting unusual or unexpected patterns of adverse event reporting that might indicate a possible safety problem with a vaccine. This way, VAERS can provide CDC and FDA with valuable information that additional work and evaluation is necessary to further assess a possible safety concern.

### Objectives of VAERS

The primary objectives of VAERS are to:

- Detect new, unusual, or rare vaccine adverse events;
- Monitor increases in known adverse events;
- Identify potential patient risk factors for particular types of adverse events;
- Assess the safety of newly licensed vaccines;
- Determine and address possible reporting clusters (*e.g., suspected localized [temporally or geographically] or product-/batch-/lot-specific adverse event reporting*);
- Recognize persistent safe-use problems and administration errors;
- Provide a national safety monitoring system that extends to the entire general population for response to public health emergencies, such as a large-scale pandemic influenza vaccination program.

[FAQs \(faq.html\)](#) | [Contact Us \(contact.html\)](#) | [Privacy \(privacy.html\)](#) |

[info@vaers.org \(mailto:info@vaers.org\)](mailto:info@vaers.org)

[USA.gov \(http://www.usa.gov\)](http://www.usa.gov) | [Centers for Disease Control and Prevention \(https://www.cdc.gov/\)](https://www.cdc.gov/) |

[Food and Drug Administration \(http://www.fda.gov/\)](http://www.fda.gov/) |

[U.S. Department of Health & Human Services \(https://www.hhs.gov/\)](https://www.hhs.gov/)

VAERS is co-sponsored by the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA), agencies of the U.S. Department of Health and Human Services (HHS).